Timely community palliative and
end-­of-­life care: a realist synthesis
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ABSTRACT
Background Community-­based and home-­
based palliative and end-­of-­life care (PEoLC)
services, often underpinned by primary care
provision, are becoming increasingly popular.
One of the key challenges associated with them
is their timely initiation. The latter requires an
accurate enough prediction of how close to
death a patient is.
Methods Using ‘realist synthesis’ tools, this
review sought to develop explanations of how
primary care and community PEoLC programmes
generate their outcomes, with the explanations
presented as context–mechanism–outcome
configurations. Medline, Embase, CINAHL,
PsycINFO, Web of Science, ASSIA, Sociological
Abstracts and SCIE Social Care Online were
originally searched. A multistage process of
focusing the review was employed, with timely
identification of the EoL stage and timely
initiation of associated services representing
the final review focus. Synthesised sources
included 21 full-­text documents and 324 coded
abstracts, with 253 ‘core contents’ abstracts
generating >800 codes.
Results Numerous PEoLC policies and
programmes are embedded in a framework
of Preparation and Planning for Death and
Dying, with identification of the dying stage
setting in motion key systems and services.
This is challenged by: (1) accumulated evidence
demonstrating low accuracy of prognostic
judgements; (2) many individuals’ orientation
towards Living and Hope; (3) expanding grey
zones between palliative and curative care;
(4) the complexity of referral decisions; (5) the
loss of pertinent information in hierarchical
relationships and (6) the ambiguous value of
having ‘more time’.
Conclusion Prioritising temporal criteria in
initiating PEoLC services is not sufficiently
supported by current evidence and can have
significant unintended consequences.
PROSPERO registration
number CRD42018097218.

Key messages
What was already known?

► The initiation of palliative and end-­of-­life

care services often requires a judgement
that a patient is approaching death,
whether it is within days, weeks, months
or a year. Such prognostic judgements are
acknowledged as irreducibly uncertain
but accepted as sufficiently reliable in the
majority of cases.

What are the new findings?

► A significant body of evidence from

systematic reviews suggests that
judgements of proximity of death often
have accuracy below chance levels.
Furthermore, a range of unintended
consequences follow from making the
identification of the end-­of-­life stage
central to providing palliative and end-­of-­
life care.

What is their significance?
a. Clinical
– Relative to current evidence, we need to
consider the implications of softening,
potentially even removing, time-­based
criteria from the sets of referral criteria
for palliative and end-­of-­life care
services.
b. Research
– Priority needs to be given to research
syntheses on: consequences of
inaccurate predictions of approaching
death; the reception of ‘bad news’
relative to findings about significant
background uncertainty of prognosis;
the effectiveness of second-­line and
third-­line therapies; and the relationship
between early referral for home care
and home death.

BACKGROUND
‘How long have I got left, doctor?’ is
perhaps the scariest and most courageous
question a patient can ask in the context
of healthcare. It is also one of the most
difficult for a health professional to
answer, both because of the uncertainty

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Review


of prediction and the intensity of emotions the latter tends to evoke. The judgement underpinning the response to the above question—a specific, even if irreducibly uncertain, temporal prognosis or a more general expectation that a patient is in the last stage of their life—is also central to health professionals’ considering transitions from curative to palliative and end-of-life care (PEoLC). It is often a key formal criterion for initiating PEoLC services.

This paper brings together evidence and lines of argumentation around the timely (or otherwise) identification of patients at the end-of-life and the timely (or otherwise) initiation of PEoLC services. This was the ultimate focus of a realist review on PEoLC programmes in primary care and/or community settings in England. The trajectory through which this final focus was arrived at is, arguably, consequential for the answers the review proposes, primarily by virtue of the sample of the literature included in it and the lens through which the latter was analysed. The original framing of the review is thus preserved as background to the study, even if the questions it provides answers to are both narrower (related to timely identification of dying patients and timely initiation of relevant services rather than PEoLC programmes in primary care and the community overall) and broader (not restricted geographically and with a relevance beyond primary and community care).

At a global level, a 2014 resolution of the World Health Assembly urged member states to ‘integrate evidence-based, cost-effective and equitable palliative care services in the continuum of care, across all levels, with emphasis on primary care, community-based and home-based care, and universal coverage schemes’. A more recent (2018) WHO document reasserted and specified this commitment further and also offered a basic model of such integration. Regional position papers, reports, research and related documents have been developed in parallel or followed on, both in high-income and low- and middle-income regions. In the context of England, whose PEoLC policy documents were central to this study, the six ‘ambitions’ for PEoLC include a community-centred ambition recognising that ‘dying, death and bereavement are not primarily health and social care events; they affect every aspect of people’s lives and experience’. In the context of the country’s primary care, the most recent general practitioner (GP) contract, in its first year (2019/2020), enabled practices to achieve 37 ‘Quality and Outcomes Framework’ points by engaging in continuous quality improvement of their end-of-life care provision, a leap from 6 points pre-2019. In view of the growing importance, complexity and context-dependence of primary and community care programmes for PEoLC, we sought to elucidate, using the principles of realist research, the mechanisms through which such programmes generate their outcomes in the immense variety of contexts in which they are designed and implemented.

METHODS

Realist research and realist synthesis

Realist syntheses (or realist reviews, with the terms generally used interchangeably) are a form of theory-based literature reviews belonging to the field of ‘realist research’ as pioneered by Pawson and Tilley. The realist synthesis approach has been specified in the scholarship of Pawson;1–14 codified in the outputs of the RAMESES projects (Realist And Meta-narrative Evidence Syntheses: Evolving Standards)15–17, and has been ramifying in the work of the latter’s team members and a growing number of committed adopters. The approach is also actively contested and advanced through the RAMESES mailing list and international realist research conferences. Work belonging or claiming to belong to the realist domain has appeared in areas as diverse as ‘development studies, social care, public health, crime reduction, agricultural extension, information science, wildfire prevention’. High level policy and funding circles are becoming increasingly receptive to it, including government departments and agencies, such as the UK Treasury, the UK Department for International Development and the US Agency for International Development and multinational organisations such as the World Bank and WHO.

Realist reviews are one of a significant number of approaches (over 30 as per) developed in the 1990s/early 2000s in response to limitations of the mainstream, Cochrane type, systematic reviews. Basic bibliometric searches in PubMed show it as one of four most widely used ‘alternative’ synthesis methods (see online supplemental appendix 1). Realist synthesis ‘always has explanatory ambitions’, is ‘firmly rooted in a realist philosophy of science and places particular emphasis on understanding causation and how causal mechanisms are shaped and constrained by social context’. A realist synthesis question is a (usually partial) version of the question ‘What works, how, why, for whom, to what extent and in what circumstances, in what respect and over what duration?’ (ibid.). This question is one representation of a fundamental assumption of realist research that ‘programme effectiveness will always be partial and conditional’ (ibid.). The outcome of a realist review is a set of middle-range theories aiming to explain how programmes cause their outcomes. The resulting causal explanations take the form of contexts–mechanisms–Outcomes (CMO) configurations. Data in a realist review are relevant if they contribute to the development, refinement and testing of programme theories and can thus come from a broad variety of sources, study types and thematic domains, including ones far removed from the topic being studied. Risk of bias is judged for the sets of evidence and arguments used in the synthesis and is not attributed to the source.
study type and/or the cumulative quality of its execution.11–15 Online supplemental appendix 1 outlines further features of the realist approach.

**Review questions**
The original questions of the review were as follows (see PROSPERO protocol CRD4201809721843 for details):
1. What are the key mechanisms which underpin PEoLC programmes for adults in primary care and community settings in the UK and similar healthcare systems?
2. How do different contexts set in motion or block those programme mechanisms?
3. What other enabling and blocking mechanisms have an impact on the outcomes of community PEoLC services?
4. How do outcomes differ across patient groups, context types and time points in the patient journey?

For realist reviews, it is ‘typical and legitimate’ for the review objectives, questions, breadth and depth to evolve as the review progresses.17 After iterative focusing (described below), we sought to offer a high-level conceptualisation in response to the above questions and answer in detail the following more specific questions:

- What are the key mechanisms which underpin timely (or otherwise) identification of patients at the end of life who may benefit from PEoLC programmes in primary care and/or community settings?
- What are the key mechanisms which underpin timely (or otherwise) initiation of relevant services?
- How do different contexts set in motion or block those mechanisms?
- How do key patient-focused, carer-focused, staff-focused and health system-focused outcomes, namely ‘good death’, quality of care, cost-effectiveness, coordination of care, hospital admissions and place of death, differ as a result of differences in the timing of identification of end-of-life stage and/or initiation of relevant services?

‘Identification’ of patients at the end of life was understood, broadly, to denote a judgement made by a healthcare professional that a patient is likely to be approaching the end of life, whether this is the last year, months, weeks or days of life, followed by adjustments to the course of care for that patient.

‘Initiation’ of PEoLC services was understood, broadly, to mean the first step that makes the transition from a mainly curative focus of care to a palliative and/or end-of-life care emphasis on comfort and quality of life.

**Review processes and stages**

**Development of rough programme theory and study protocol**
A key task at the outset of a realist study is the constructing, or ‘surfacing’, of an initial (rough, candidate) programme theory.24 25 ‘Programme theory’ is the description ‘of what is supposed to be done in a policy or programme (theory of action) and how and why that is expected to work (theory of change)’.24 At the end of a realist review, a programme theory needs to be couched in CMO terms and serve to explain ‘how and why different outcomes are generated in different contexts’.24-25 We developed an initial programme theory primarily through within-team discussions (diagrammatic representation in online supplemental appendix 2). Two team members were content experts in PEoLC (SB and MP), two (SB and GW) were practising GPs, and one team member (GW) was an experienced realist reviewer (the other two core team members, IK and IW, were, respectively, a library and information specialist and an evidence synthesis researcher with a clinical background). Foregrounding conceptual challenges in the discussions were how to circumscribe ‘a programme’ and how broadly to cast the net in defining ‘community’ (see box 1 on the understanding of ‘community programme’.

**Box 1 What is a community programme?**

A programme had to have one or more of the following features to be considered a ‘community programme’:

- Delivered fully or primarily in settings different to hospital inpatient or hospice inpatient settings—that is, settings which are (1) closer to the day-to-day life of patients and thus, arguably, more accessible or reassuringly familiar and (2) relatively ‘low-tech’ and thus, arguably, associated with lower costs of care.
- Prioritising respect for the value, dignity, rights, choice, will, self-knowledge, self-determination, etc of patients as opposed to treating them, even with the best of intentions, as primarily vulnerable and passive recipients of care.
- Developed through engaging patients and communities.
- Drawing significantly on the resources of informal social networks and activating non-medical contributions to quality of life—for example, compassionate and pragmatic daily care; watchful presence; solutions that are sensitive to the cultural or other group identity of a patient and are attuned to the strengths and limitations of the local context.

**Treatment of key types of boundary cases:**

Home-based, day care and other non-inpatient programmes delivered by hospital, hospice or specialist palliative care teams were included; care home programmes were included.

**Substance—surface tension:**
As only one of the above features was sufficient to identify a programme as a ‘community programme’, some of the initiatives we have included would not be considered ‘proper’ community programmes under stricter definitions, that is, ones aiming to exclude all cases of ‘tokenistic’ involvement.

**Local—global perspective:**
In the UK and other high-income countries, social institutions are, overall, better established and stronger than those in low- and middle-income countries. This is often believed to be paralleled by greater independence of the members of a given community from one another and of the community as a whole. As such, the community programmes we reviewed may have, on average, stronger formal structures and links with social institutions than would be the case in more traditional societies. They might also be less influential by virtue of having, typically, a range of statutory alternatives.
consolidated in the course of the work). Key UK policy documents on palliative, end-of-life care and community care were also consulted. Two stakeholder groups were engaged: a study-specific professionals’ advisory group and a patient and public involvement (PPI) Group with a broader remit (detail in online supplemental appendix 3).

Literature searching and initial screening

Online supplemental appendix 4 describes in detail the approach to literature searching and screening. Briefly, our main search strategy combined four blocks of search terms around: (1) PEoLC; (2) primary and community care; (3) UK (which reduced non-UK sources but still captured a significant number of them) and (4) programme (theory, model, philosophy). Limiting to UK sources served to circumscribe, in a way that ensured coherence of the macrocontext, the policy, health services setup, financial and community context of programmes. However, no restrictions on origin or language of papers were placed. As long as they helped to test and refine the evolving programme theory, they were included for further consideration. We searched Medline, Embase, CINAHL, PsycINFO, Web of Science, ASSIA, Sociological Abstracts and SCIE Social Care Online. Records between 1998 and 2018 were used, 10 years either side of the 2008 End-of-Life Care Strategy for England. The resulting dataset was of 2832 citations.

Relevance of a piece of evidence in the realist approach is determined by its capacity to enable the testing and refinement of the programme theory. As the theory itself is under development, judgements about relevance are partly dynamic and underdetermined. While we were guided by the set of inclusion-exclusion criteria outlined in the protocol (briefly: adults whose death is perceived as imminent or who have advanced, progressive or incurable conditions; programmes, interventions, initiatives, approaches, tools, etc for the provision of PEoLC in primary care and other community settings; no restrictions on study design, non-empirical research also included), we worked within flexible boundaries of relevance. In the screening process, we classified abstracts into tiered inclusion and exclusion categories, reflecting different levels of perceived relevance (eg, ‘core contents’, ‘include, generic’, ‘include, broad’). The ‘include, broad’ category, in particular, contained references that went beyond our explicit inclusion criteria (eg, from other countries, settings, conditions, age groups) but pointed to potentially transferable CMO-elements or configurations. A range of targeted searches were also conducted as the study progressed (see online supplemental appendix 4).

Data extraction, analysis and synthesis

After screening 1226 citations (title, abstract, keywords; alphabetical order of first author surname within chronological order) out of the main dataset (of 2832 citations), we reached a level of saturation of emerging issues. This was taken as an opportunity to use roughly half of the dataset for theory development and refinement and the other half for theory testing. Data extraction—in the form of document coding—was then initiated. Using NVivo (QSR International, V.12), we coded with a high level of granularity the abstracts of all citations tagged as ‘core contents’ or ‘potentially core contents’ during the screening (253 citations, over 800 codes). To achieve greater accuracy, systematicity and transparency of the process of extracting data from the primary studies and including them into the synthesis study, we annotated substantive codes with what we called ‘bridging terms’. The latter linked the form in which the data appeared in the original study to the CMO configurations expected as an outcome of a realist study. For instance, MMEAN—standing for “Mechanisms, Meanings, Experiences, Attitudes, Narratives”—indicated that the original study relied on concepts such as ‘meaning’ or ‘experiences’ and that its findings can underpin the formulation of a realist mechanism.

Next, we reorganised the NVivo codes into eight broad categories representing types of PEoLC programmes (see Findings). We sought to develop categories by abstracting high level CMOs from the specific CMOs characterising the programmes described in the literature. Apart from taking the analysis at a higher conceptual, realist-informed, level, this was an attempt to contain and focus the work. Further narrowing of the review focus was, however, required. The steps taken to achieve it aimed to balance the following tensions:

1. Clear focus—preservation of aspects of the big picture envisaged in the original review questions.
2. Priorities in policy documents—priorities in the research literature.
3. Practical importance—conceptual promise.
4. Relevance to the practice of professionals—resonance with lay persons.
5. Richness of data—feasibility of their analysis.

The time and timing theme was chosen as a focus for the review, as it met the five criteria above better than any other candidate theme. As, on closer inspection of the main dataset, we found that time and timing was still too broad a topic, we went through a succession of further stages in narrowing the review focus. We mapped discussions of time and timing in the retrieved research literature against discussions of the same concepts in five key national policy documents and/or reports.7 26–29 We took the overlap of interest to represent shared priorities, including:

1. Timely identification of patients who are approaching the end of life, typically seen as prompting the timely initiation of relevant services.
2. What we termed ‘temporally defined services’ (such as 24/7 services, rapid response services, out of hours, night sitting, fast track discharge).
3. Advance care planning.
4. The final race against time to respect a dying patient’s wishes.

The decision to focus on identification (topic 1 of the four above) was driven by the relative richness of evidence in our dataset (higher for topics 1 and 2 than for 3 and 4); the fact that identification of the end-of-life stage was the first step in a new pathway of care; and, finally, the strong negative reaction we received to some of the findings from the PPI Group, perceiving them as damaging to the need and right to be appropriately prepared for death, should health professionals be aware of an impending death. We felt that finding clear and effective ways to represent this subset of the study findings is important. See online supplemental appendix 3 for details on stakeholder involvement.

Figure 1 represents graphically the process of focusing the review, including sub-stages not discussed above. Figure 2 represents a modified PRISMA diagram.

**FINDINGS**

The Findings section consists of two largely independent parts. Box 2 represents a classification of PEoLC programmes in terms of their overarching logic of mechanisms causing outcomes, as developed through the coding of ‘core contents’ abstracts. This is a relatively abstract, conceptual response to aspects of the original review questions. The narrative part of the Findings section concerns only the narrow review focus on issues around timely identification of patients approaching the end of life and the associated initiation of services.

Timely identification of the end-of-life care stage and timely initiation of services

In the remainder of the Findings section, we argue that current PEoLC policy in England is underpinned by a rough programme theory of Preparation and Planning for Death and Dying whose CMOs can be very powerful, but are also often enough blocked,
counteracted, neutralised and even distorted by CMOs arising from the directions of: (1) uncertainties and unknowns in predicting death and dying; (2) orientations towards Living and preserving Hope till the very end; (3) grey zones between palliative and curative care; (4) complexity of decision making about referrals; (5) the loss of pertinent information in rigid hierarchies of knowledge and labour; (6) the ambiguous value of having 'more time', which can enable patients and carers to prepare, achieve closure, enjoy each others' presence for longer, but can also be 'more of a difficult time'.

Preparation and planning for death and dying: the current policy discourse
Timely identification of patients who are likely to be approaching death, often understood as the last year of their lives, opens up precious opportunities to discuss, plan and organise care around a patient’s needs, wishes and preferences, for instance, around preferred place of care or death and the invasiveness of treatments attempted; around the capacities and needs of the patient’s loved ones and/or other informal carers; the features of the patient’s home or other relevant environment; the availability of local services; and with a view to the sustainability of the healthcare system (eg, by seeking to reduce unnecessary admissions and interventions).27–29

Outside of the immediate context of healthcare, awareness that death may be near enables patients to put their affairs in order; make the best of the time they have got left; complete what has been left undone or find better closure for it; settle and heal relationships; express feelings such as love, regret, forgiveness, gratitude and appreciation; reminisce about their life and find a sense of value and meaning in it; and leave a legacy for future generations.30–31

In contrast, delayed identification of the end-of-life stage may mean that patients are robbed of time they believed they had; be denied the opportunity to have a choice in how and where they die; experience significant distress and, ultimately, not have the death they wanted. Families and other people close to the patient may also feel robbed of time and choice; go through avoidable distress and traumatic experiences around the time of death; and be left to deal with feelings such as guilt and complicated grief for years to come.26 27

Delays and omissions in identifying dying patients often result from insufficient knowledge, experience, confidence and associated training—one aspect of a much broader problem of knowledge, skills and training in PEoLC.26 27 They also reflect deep-seated challenges around information sharing and care coordination.32 Disease trajectories also have an impact, potentially irreducible, for example, the trajectories of heart disease or respiratory conditions are less predictable than those of cancer. The transition into the end-of-life stage is also frequently difficult to identify for frail older patients or people with dementia.26 27

Detailed CMO configurations and associated evidence can be found in online supplemental appendix 6: table 1, sections 1.1, 1.2 and 1.3.

Low accuracy of prognostic judgements in PEoLC
The mainstream Planning and Preparation framework, as summarised above, relies on the assumption that prognosis at the end of life is sufficiently accurate, even if uncertainties are openly acknowledged.7 26 Evidence from systematic reviews contradicts this assumption strongly. Out of 20 studies reporting on categorical survival estimates in a systematic review by White et al,33 only two demonstrate overall accuracy of prognosis over 70% while in 12 studies it is below 50%. In a systematic review on the Surprise Question (‘Would I be surprised if this patient died in the next 12 months?’) Downar et al34 estimate pooled positive predictive value (the proportion of patients who died when the clinician predicted dying) of 37.1% (95% CI 30.2% to 44.6%). No improvements are visible from oldest to newest studies, which could have been expected in view of advances in diagnostic/prognostic technologies and medical education. No consistent evidence has been found on the impact of professional group, level of experience or time frame of prognosis (eg, imminent death vs within 12 months) on the accuracy of prognosis.33 35

Prognostic judgements are made through various combinations of probabilistic objective criteria, clinical judgement and/or subjective intuitions.36 A variety of prediction modalities and frameworks are used by health professionals of different professional backgrounds, of different levels of skills, experience and confidence, with different degree of input from other professionals.33 36 Prognostic judgements are made of
Box 2  Types of palliative and end-of-life care programmes in primary care and the community in terms of broad programme logic expressed as context–mechanism–outcome (CMO) configurations (brief, see online supplemental appendix 5 for complete box)

Type 1 programmes: Programmes seeking to improve the availability of services where systemic and critical gaps exist: in terms of time, location, intensity and responsiveness (when, where, how much and how quick)
When palliative care is needed in time periods outside of normal working hours and in underserved areas (C), end-of-life care outcomes will improve dramatically and efficiently (O) only if services are time-of-the-day-independent (M), flexible (M) and responsive (M).

Examples of type 1 programmes that address time and timing
► 24/7 services
► Out of hours (OOH) services
  – OOH specialist palliative and end-of-life care services
  – OOH pharmacy provision of drugs
  – OOH generalist services
► ‘Informal’ OOH services (eg, general practitioner (GP) providing personal phone number)
► ‘Twilight’ services (in the underserved periods between daytime and OOH services)
► Night services
  – Night nursing
  – Night sitting
► Hospice day care services
► Rapid response services

Examples of type 1 programmes that address location, coverage and proximity
► Home-based services, including hospice at home
► Hospice outpatient services
► GP practice palliative and end-of-life care clinics
► Community centres services
► Host family respite
► Rural services
► Telecare services
► Deprived areas services
► (Relative) services moving closer to the users

Examples of type 1 programmes that address intensity and responsiveness
► Rapid response services
► Improved standard practice (new types of prioritisation)

Type 2 programmes: Programmes defined through the broad aspect of our humanity and needs being addressed, often as forms of care and support provided by a particular professional or lay group (detail in online supplemental appendix 5)
As suffering and pain are multimodal (C), we can achieve better quality of life for dying patients (O) when we acknowledge the numerous modalities of experiencing pain and suffering and by acting in (more) holistic ways (M).

Type 3 programmes: Programmes addressing the management of boundaries and transitions
As the needs of dying patients at transition points can be extra complex (C) and different services often lack sufficient levels of integration and coordination (C), we can enable each patient to receive the most appropriate and timely care within resource limits (O) if we manage service boundaries and transitions better, in rational yet person-centred ways (M).

Examples of type 3 programmes that address discharge management
► Rapid hospital discharge to enable home death
► Discharge roles (eg, discharge community link nurses)
► Discharge letters and templates
► Discharge policies and pathways
► Discharge practices when palliative care needs reduced or prognosis modified

Examples of type 3 programmes that address referral management
► Clarification of referral criteria (triggers) and development of documentation
► Rules on referral initiators—who can refer?
► Rules on referral timing—when to refer?
► Referral triggers—what needs to happen so as to refer?
► Referral audits for quality improvement

Examples of type 3 programmes that address ‘midway solutions’ between service types
Continued
Box 2  Continued

- Intermediate care beds
- Community hospitals
- Hospice at home services
- Primary care doctors with visiting rights to local hospitals

Examples of type 3 programmes that address the management of transitions and working across settings
- ‘Alignment models’, for example, aligning the work of GPs and care homes
- Bridging roles—liaison roles, secondments, dual roles
- Case reviews across settings
- Electronic data sharing, Electronic Palliative Care Coordination Systems (EPaCCS)
- Hand-over protocols and forms, particularly for OOH
- Multidisciplinary team meetings
- Service integration work
- Transportation across settings
- Partnerships between ambulance service and other settings

Type 4 programmes: Programmes prioritising patient-centredness, ownership and empowerment (detail in online supplemental appendix 5)
As patients and their carers have a range of diverging end-of-life care needs, preferences and wishes (C), we are far more likely to achieve the goals of care that truly matter to them (O) if these are clearly elicited, recorded and acted on (M) and, more broadly, if services are codeveloped with patients and carers (M).

Type 5 programmes: Programmes addressing different phases of an illness or of the dying process (detail in online supplemental appendix 5)
As the phase of an illness and/or proximity to death have a profound impact on patients’ treatment and care needs (C), we can improve patient outcomes and support the sustainability of the health service (O) by structuring and delivering services in a phase-centric way, which enables service optimisation, with no relevant needs missed and no unnecessary activities undertaken (M).

Type 6 programmes: Programmes taking a systemic approach
As the terminal phase of an illness or the process of dying can be very complex and fast changing and involve a large number of services (C), we are more likely to achieve positive outcomes for the patients, their family and the system (O) and less likely to encounter crisis situations (O) if terminal illness and/or the process of dying is approached in a systematic, proactive and anticipatory manner rather than a piecemeal and reactive one (M).

Subtypes and examples

Programmes aiming to improve identification of patients in need of palliative and/or end-of-life care
- Development of new prediction and risk stratification tools
- Broader, more systematic implementation of prediction and risk stratification tools
- Improving staff abilities in identifying patients at the end-of-life
- Improving the skills of junior and lower level staff in communicating concerns about patients higher up the hierarchy
- Appropriate recording and communication of such information to other services, for example, through Registers (EPaCCS)

Programmes enabling discussions of death, dying and care at the end-of-life

Programmes aiming to improve advance care planning (ACP)
- Tools, pro formas, templates
- Enhancing basic staff skills in using them
- More in-depth training on using ACP tools, acknowledging challenges such as differences between family and patient preferences, dynamics of preferences, service limitations, creating the right environment for the conversations, etc
- Initiatives to support the broader, more systematic use of such tools

Programmes aiming to improve integration of care and handling diffusions of responsibility
- Case management initiatives
- Key worker initiatives
- Data sharing for improved informational continuity
- Palliative care coordination centres
- Bridging roles

Programmes aiming to develop or refine existing protocols and pathways

Programmes based on the use of decision-making tools

Programmes aiming to improve monitoring and evaluation systems and processes

Continued
Box 2  Continued

- Enhanced annual reviews of patients
- Patient recall systems and processes
- Palliative and end-of-life care registers and dashboards
- Provision of (comparative) data on palliative and end-of-life care processes and outcomes

Programmes facilitating internal change through external support
- Peer facilitation for practices
- Educational facilitation

Programmes creating a broad supportive environment
- Financial incentives
- National guidance
- Local change management initiatives
- Identifying and supporting ‘champions’

‘Meta-programmes’—highly systematic ways of developing new local initiatives and programmes

Type 7 programmes: Programmes seeking improvements through staff and volunteer development (detail in online supplemental appendix 5)
When work environments value palliative and end-of-life care training and development as part of their business-as-usual rather than a matter of short-term projects (C), palliative and end-of-life care provision across the board improves (O) through investment in the knowledge, skills, motivation, attitudes, etc of professionals and lay persons providing care (M) and through creating effective role structures and arrangements (M).

Subtypes and examples

Programmes based on developing new staff roles and forms of task distribution
- Extended nurse prescribing in palliative care
- Peer facilitators with ‘dual roles’ (e.g. GPs with special interest in PEoLC)
- Bridging roles

Programmes for staff training and support
- From palliative care specialists to generalist staff
  - Training in specific skills
    - Communication
    - Palliative and end of life care prescribing
    - Advance Care Planning
  - Training for specific staff groups
  - Training by using different approaches, contexts and platforms (hands-on, online, on-the-job, etc.)
- Support for generalist staff, or even specialist staff, in dealing with rare diseases

Programmes expanding the roles of volunteers and community members
- Compassionate cities initiatives
- Volunteers in hospices
- Death dealers

Type 8 programmes: Programmes defined through the support they provide to informal carers
The presence of carer-focused programmes in the research literature, as sampled, was not on a par with the presence of programmes of the other seven types. Further research is needed on the degree to which support for informal carers in palliative and end-of-life care translates into programmes which are defined in terms of their carer-focused mechanisms rather than including them as a secondary component.

Note: Here, we offer a typology of palliative and end-of-life care programmes in primary care and the community in terms of the overarching, generic theory (taking the form of a CMO configuration) to which they appear to subscribe. We have abstracted the high-level, generic CMOs from specific CMOs characterising the example programmes analysed, with the examples coming from the 253 ‘core contents’ citations. For instance, on the basis of the brief programme descriptions we have reviewed, we suggest that the abstract mechanism underpinning innovative discharge roles is the management of boundaries between services and settings. Similarly, we suggest that intermediate care beds can be thought of as a boundary management initiative—both between service types (hospital and community) and patient needs (requiring intense professional input and oversight—requiring more limited professional input and oversight). Thus, two programmes which may ‘look’ very different belong, in our classification, to the same type by virtue of their shared theoretical underpinning—shared programme logic of mechanisms causing their outcomes. Further work is required to elicit the theories behind the specific programmes included here and to test our choices of a ‘defining theory’. Online supplemental appendix 5 presents the complete box. More intuitive parts of it have been condensed in this version.
patients in different phases of an illness or frailty. Judgements about individual patients are also made in complex, dynamic and often overburdened healthcare contexts. Powerful emotional factors also come into play, such as health professionals’ reluctance to share bad news; the value of hope for many patients and their loved ones; or some health professionals’ resistance to ‘admitting failure’ in not being able to do more for a patient.

A targeted search of systematic reviews on prognosis we conducted (key data extracted from the abstracts of 71 reviews) identified a vibrant research field. However, the emerging picture is of significant complexity and distance from clinical applications.

Detailed CMO configurations and evidence associated with prognostic judgements can be found in online supplemental appendix 6: Q5 and Q13; 1.4 and 2.6.1 in table 1; and table 2.

Personal cost of inaccurate prognosis
Relative to such findings, the current discourse on timely identification at the end of life, while rightfully eloquent about the consequences of delayed identification, appears surprisingly quiet on the emotional, ethical, pragmatic and other effects of inaccurate predictions of proximity of death (no relevant evidence in our sample). Stakeholders shared anecdotal evidence of exhaustion and emotional turmoil experienced by carers years after a family member had been given ‘weeks’ to live. Survivors pointed out the burden of handling other people’s reactions at a time when they were ‘written off’. The literature on receiving bad news in a medical context and of differing responses to such news may acquire new light relative to findings about significant background uncertainty of prognosis as opposed to the frequent invocation of ‘denial’ in PEOlC.

Expanding grey zone between curative and palliative care interacting with patient wishes
The increasing availability of curative therapies, for example, for cancer, and of oral preparations in particular, contributes to later and later referrals to PEOlC, as there is almost always a further line of therapy that can be tried. Circa 2007, Mintzer and Zagrabe identify 26 agents approved by the FDA (Food and Drug Administration) in the preceding decade which have come to be used routinely for the treatment of a variety of malignancies. As of August 2021, the A to Z list of cancer drugs of the National Cancer Institute (USA) lists 641 approved drugs for cancer or conditions related to cancer.

Only a small proportion of patients appear to respond to such therapies and with minimal gains. As a result, many patients die without receiving any, or adequate, palliative care. Overall, patients may experience a prolongation of suffering rather than life. In view of such outcomes, non-palliative professionals, for example, oncologists, who initiate such courses of action may be judged as overly aggressive in treatments at the end of life; resistant to palliative care; overly committed to a curative ethos and likely to perceive death as a failure; driven by a mindset of having to do something because they are expected to or feel responsible to find a solution; even driven by a hubris that they hold God-like power at the life-and-death line. Such mechanisms and contexts, however, interact in complex ways with far more patient-driven ones. The outcomes are identical or similar to those explained by health professionals’ resistance to a palliative care ethos and related reasons. The leading driver of decisions to continue with curative treatments are often the wishes of the patient and their family rather than a non-palliative professional’s clinical judgement and recommendation. Following such wishes, rather than aiming to influence the reasoning of patients and carers, is a meaningful choice when new treatment options are available and increasing; when there is always the off-change, the 1% uncertainty, the miracle recovery even; and when hope till the very end is of immense value for some patients and families. An inclination to respond to patient and carer wishes and preferences for trying once more may, again, be rendered more likely by a non-palliative professional’s own difficult emotions. (op. cit.)

CMO configurations and evidence associated with the grey zone between palliative and curative care in online supplemental appendix 6: table 1: sections 2.6 and 2.6.1.

Complexity of decisions about referrals to PEOlC services—further factors
Family needs
The needs of the family and informal carers may be a far more consequential factor in referring to specialist palliative care services than a health professional’s judgement about a patient’s likelihood to be at the end of their life. An aspect of this is that some families decline early offers by generalist staff to involve specialist community services (op. cit.).

System-level factors
A broad range of system-level factors also affect referrals. These may include perceptions of excessive workload/ limited capacity of the specialist community services or lack of confidence in the quality of their work. Concerns of overspending may be a consideration. The very act of referral is not straightforward either: technical problems may arise with electronic referral systems or the level of detail required may be experienced as off-putting (op. cit.). With individual services rarely covering every need of a patient and their family, a particular referral is often only one element of a complete package of care to be activated only if the whole package can be put in place. (op. cit.)

Potential overconfidence in own abilities
There are some indications in the literature that generalist staff may perceive their PEOlC knowledge and
ability to deal optimally with dying patients as better than they actually are, resulting in fewer or later referrals to specialist services than beneficial for patients. Evidence in our dataset was insufficient to make a strong claim (see online supplemental appendix 6, 4.3.1.1), yet it is possible that brief training events for generalist staff—often part of a strategy for improving PEOiLC knowledge and skills—raise confidence in their recipients’ knowledge and skills more than they raise knowledge and skills.

CMO configurations and evidence associated with factors contributing to the complexity of decisions about referrals in online supplemental appendix 6: table 1, sections 2.2, 2.3, 2.3.1, 2.4 and 2.7.

Reverse engineering of predictions
Temporal criteria in access to PEOiLC services have aimed to increase equity, yet referral criteria also serve to manage demand for an enhanced type of service. When a health professional is committed to do one’s best for a patient and/or the family is actively, persistently seeking help, referring professionals may ‘reverse engineer’ the uncertainty of predictions at the end of life (online supplemental appendix 6: table 1; Table 1, 1.7). They refer a patient to a service by claiming a shorter prognosis than they believe to be accurate. I.e. they ‘play the system’ so as to ensure the best possible care for their patients while the well recognised uncertainty means that they are making no demonstrable error of judgement.

Hierarchy of knowledge and labour
Staff such as healthcare assistants, care aides, personal support workers who provide hands-on care to patients may make highly accurate observations of less conspicuous changes to the patient’s condition, allowing them to predict a transition towards the end of life. However, their input is often ignored, as they are considered low-level personnel without the training and skills needed for such judgements. Time pressures for senior staff exacerbate the tendency (online supplemental appendix 6, 1.5).

Experiences that fill up the time enabled by early identification
Reasoning within the Preparation and Planning framework shows awareness that ‘early identification’ can have its own dangers. It is one of the reasons why ‘timely identification’ is often a preferred term. Still, the leaning of ‘timely’ is in the direction of ‘early’ and the framework does not unpack the potential downsides of early identification.

Early identification of symptom control needs may result in patients being perceived as chronic disease patients rather than approaching the end of life. As a result, they may receive less input from specialist community services, as data in Addington-Hall and Altmann 2000 suggest. Early referral to services supporting home care may also, in some cases, reduce the likelihood that a patient dies at home. This may be because families and/or professionals find it difficult to sustain care at home for extended periods of time.

A significant time lag between diagnosis and referral to a palliative specialist (in this sense late referral) may, paradoxically at first sight, increase the likelihood that a patient dies at home. Patients may have developed greater acceptance of their terminal prognosis because they have been ‘through more trials, tribulations, and treatment failures, and spent more time in institutions’. They may thus be more likely to seek, accept and plan for home-based palliative care as opposed to more invasive, hospital-based care with curative or life-prolonging goals. From such a perspective, there are individuals for whom trying anything other but palliative care is a precondition for palliative care being seen in a positive light.

CMO configurations and evidence associated with the above theme can be found in online supplemental appendix 6: table 1, sections 1.6, 2.9 and 2.10.

DISCUSSION
Summary of main findings and comparison with existing literature
This realist review addressed programmes for PEOiLC for adults in primary care and community settings, with a further focus on issues around timely identification of patients who are at the end of their lives and the associated timely initiation of services. The key outcomes of the review are:

1. A working typology of PEOiLC programmes (and, to a degree, routine services) in primary care and the community, which condenses their immense and often confusing variety. Using a realist logic, we have aimed to centre the typology around ‘deeper’ similarities between programmes (eg, of how and why they are expected to work) rather than more ‘surface’ ones (eg, what visible activities are carried out and where). The typology needs further development and refinement but, we suggest, already enables more reliable comparisons in programme evaluations and commissioning decisions.

2. An argument—an evolving realist theory comprised of interacting CMO configurations—that calls into question a foundational assumption underpinning a broad range of PEOiLC policy and services, namely that an accurate enough, be it irreducibly fallible, identification of patients approaching the end of life is typically achievable. As should be desired of a literature review, this review has both significant overlaps with the existing literature and an original, ‘meta-level’ perspective which makes it a whole—a synthesis—that is greater than the sum of its parts. The crux of our argument around patient identification used ‘ready’ evidence from pre-existing systematic reviews which, however, acquired new force once embedded in a broader argument. This broader argument brought to light tensions between accumulated evidence on prognosis, on the one hand, and PEOiLC practices and policies predicated on early or timely identification of the dying stage, on the
other. Some of the unintended consequences of this policy-evidence mismatch are a cause for concern. The argument also guarded against easy appeals for ‘further research’ and ‘improved tools’. Having consulted over 70 systematic reviews on prognosis from the last 5 years, we suggested that dramatically improved prognostication tools suitable for clinical practice may be a long way away and possibly an unachievable ‘holy grail’.

The CMO configurations we presented as acting consistent with the Preparation and Planning framework (under themes such as orientations towards Living and preserving Hope; grey zones between palliative and curative care; complexity of decision making about referrals, etc) are, realistically, familiar to professionals and congruent with the background knowledge of PEOlC researchers. They are also well represented in the research literature, far better than the need to contain this work allowed us to demonstrate. Yet they too received a combined force and meanings they did not possess in isolation. Similarly, the interim focus of the review on ‘time and timing’ constructed a new composite object of inquiry. Time and timing motifs are omnipresent in palliative care for patients with dementia, music therapy, meaning of life interventions, social capital in end-of-life care for patients with dementia and hospice at home, suggest that realist synthesis tools suitable for clinical practice may be a long way away and possibly an unachievable ‘holy grail’.

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**Strengths and limitations**

The originality and potential practical importance of the study outcomes was enabled by a robust yet adaptive process, emphasising rigorous transitions in narrowing the study focus and honing further the tools of realist synthesis. Some of the steps we took (eg, the use of ‘bridging terms’; the mapping of the field on the basis of abstracts coding; the extra systematic approach to focusing the review) were not part of the conventions of the realist review approach but, we believe, are consistent with it and may contribute to its methodological toolkit.

A significant weakness of the review is that the study-final theory around timely identification is, while validated by professionals and subject specialists, tested against a sufficiently broad range of evidence only in the aspect of prognosis. Most of its other aspects are at the level of theory development based on indicative evidence rather than at the level of extensively tested CMOs. Furthermore, our explorations into candidate ‘substantive’/ ‘formal’ theories (briefly, the theories developed within scholarly disciplines to explain specific phenomena in their field of study), whose effective use is seen as a marker of quality in a realist review, did not bear fruit. Next, the process of constructing the review focus may have been too complex for a relatively small study. The quest for the perfect focus may have led, paradoxically, to suboptimal focus. Some of the steps of this process, for example, the use of abstracts, were also contentious. Finally, a realist review is significantly different from a mainstream systematic review approach and some of its particularities can be perceived as methodologically substandard. Online supplemental appendix 1 represents some of the decisions taken in this review through the critical lens of a mainstream systematic review and aims to bridge the gap.
Box 4 Implications for practice—initial recommendations and reflections

The following recommendations and reflections seek to translate the review findings into initial responses to the question of ‘what to do then’. Solid proposals for changing non-evidence-based practices around patient identification and initiation of palliative and end-of-life care services require further consideration and assessments for acceptability, feasibility, impact and unintended consequences.

1. Consider the implications of removing, or at least softening, time-based criteria from the sets of referral criteria for palliative and end-of-life care services. Current evidence is quite clear that, on average, they are fallible while also associated with important unintended consequences.

2. Routine data can be used to conduct local, even clinician-specific, evaluations of overall accuracy of prognosis if the evidence presented here is considered insufficient. Such evaluations can use, for instance, Electronic Palliative Care Coordination Systems and the dates of adding patients to them (when identified as end-of-life) relative to the dates of ‘deducting’ them (after death). Similarly, the date of first prescribing ‘just in case’ medications can be linked to the date of death of a patient.

3. Increase and diversify the triggers which set in motion the following processes, often associated with preparing for death or the provision of palliative and end-of-life care:
   - Data sharing preferences.
   - Assessments for psychological, social and spiritual support needs in the face of experiences of deep vulnerability (of which mortality is a key aspect, but not the only one).
   - Elicitation of preferences for home care and home care support needs.
   - Carer needs assessments.
   - Discussions of preferences for care in situations in the future when mental capacity may be lacking.
   - Discussions of ceilings of care.
   - Detailed assessments of pain relief and symptom control needs.

Addressing such needs should not be triggered primarily in association with proximity to death. Nor it needs to be done necessarily, or even preferably, in the context of palliative and end-of-life care services. Skilled health professionals both within and outside of palliative and end-of-life care already attend to such needs regardless of a patient’s prognosis and the context of care, but may be impeded by system fragmentation, policing of boundaries between specialties and demand management criteria, among others.

At a conceptual level, the definition of palliative care is also broadening towards ‘serious health related suffering’ and away from life-limiting illness, death and dying.51 The flipside of this is that serious health related suffering is not the sole provenance of palliative care. There is much in palliative and end-of-life care that is ‘just good care’.

1. Explore (further) one’s personal standing relative to conversations on time-limited prognosis, death and dying in light of the tension that, on the one hand, current evidence suggests that the accuracy of prognosis is often limited and, on the other, immense negative consequences can arise if a death is completely unexpected till the very end.

There is no easy answer to the question of how we acknowledge the prospect of death and dying as a very real, very proximal experience and, as a result, benefit from preparing for it, while also preserving hope for a longer life, if valued. The dilemmas are exacerbated by the tension that health professionals know far more about the signs of irreversible deterioration and death than most patients, yet have far less of the certainty that patients may want, expect and even demand. Positioning oneself relative to such dilemmas has an irreducible personal component. No level of training and professional guidance can fully substitute for it.

2. The overall unsatisfactory accuracy of prognostic judgements should not become an excuse for avoiding difficult conversations about death and dying—with others and oneself.

3. There will be significant economic consequences to removing temporal criteria in referral to specialist or enhanced palliative and end-of-life care services. These may be difficult to quantify and exceptionally difficult to meet, yet we cannot be avoiding them by pretending temporal criteria are sufficiently objective, neutral and fair.

Implications for practice

Crucially, we argue that the presence of powerful CMOs which are oppositional to the framework of Preparation and Planning for Death and Dying is not a reason to disinvest—ideologically, emotionally, financially, etc—from it, but to complement and balance it in creative ways, even if the approach taken may appear as backtracking on important advances in open discussions of death and dying. We may be able to achieve better end-of-life care, faster, if we enable specialties, settings and health professionals committed to a life-saving, curative ethos to integrate more of our processes, structures and skills without making them about the end of life. See Box 4 for initial recommendations and reflections.

Implications for research

The explanatory framework we are proposing will be tested most robustly and expanded most fruitfully by research synthesis studies (realist or other) on: the emotional, ethical, pragmatic and other effects of inaccurate predictions of proximity of death; the reception of ‘bad news’ relative to findings about significant background uncertainty of prognosis; the effectiveness
of second-line and third-line therapies; and the relationship between early referral to services supporting home care, on the one hand, and home death, on the other.

CONCLUSION
PEoLC programmes in primary care and community settings are here to stay and grow. A realist perspective centred around the concepts of CMO offers a promising way of understanding and improving their workings. Once again, however—after decades of seeking to expand palliative care outside of the realm of cancer—we may need a significant rethinking of the reach of PEoLC programmes. A significant pool of evidence on prognosis suggests that current end-of-life care policy in England and any other country which relies strongly on ‘timely identification’ is nothing short of hubristic in its expectations of working out Death’s timings. And while the day may come, for better or worse, when we are able to perfect the latter, for now we will achieve more if we focus on other ways of improving the end-of-life care we provide, no matter how brief or how long we are providing it for.

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REFERENCES
18 RAMESES JISCM@il list. Available: https://www.jiscmail.ac.uk/cgi-bin/webadmin?A0=RAMESES
attachment_data/file/879438/HMT_Magenta_Book.pdf [Accessed Sep 2020].

21 Cant S. RAMESES JISC\@ all list discussion, 20 Aug 2020. Post in thread on “Best reference to convince reviewers of strength of realist paradigm."


Box 1: More on realism

1a. Realism, in the intellectual tradition of Pawson and Tilley, is characterised by the following assumptions*:

1) Both the material and social words are “real”; anything that can have real effects is real – crucially, this claim is intended to take a stance on the traditionally controversial reality of constructs and entities such as culture, gender, social class, programmes, policies, social institutions, ideas, etc.

2) Mind-independent and interdependent reality – both the natural and social world exist and exert their powers independently of our understanding, judgements and interpretations of them, but they are also affected by human actions based on the latter (in this sense, have a reality interdependent with our ideas).

3) All enquiry and observations are “filtered through” the human mind; therefore, there is no “final” truth or knowledge. However, we can still work towards a closer understanding of reality because reality constraints our interpretations and we can continuously test, judge and refine them.

4) All social systems are open systems – social systems interact and influence one another and change over time, producing outcomes with or without the introduction of a policy or programme. A realist study can only show that a policy or a programme contributed to an outcome.

5) Realism subscribes to a "generative" view of causality (Bhaskar, 1975, Pawson, 2008) in the sense that, briefly, observable outcomes are generated by largely non-observable causal processes and forces (mechanisms), which operate or not depending on the contexts in which they occur. As a result, outcomes vary across different contexts. Realist research aims to identify the mechanisms which cause outcomes, not just associations between programmes and outcomes.

6) Whether mechanisms generate outcomes depends on the context in which they function – realist research identifies what it is about the context that determines whether, and which, mechanisms “fire”.

7) Mechanisms operating in different contexts generate different outcomes – programmes thus generate different outcomes for different groups of people in different contexts, with realist research aiming to identify and explain different outcome patterns.


Box 1: More on realism, continued

1b. Other “realisms” and other realist philosophies of science

While versions of the positions described in 1a. are standard in the realist research community circumscribed as above, such an interpretation of realism becomes problematic, or at least too facile, when mapped against debates on realism (including distinctions between realism about the world and realism in the philosophy of science), causality, mechanisms, explanation, theories, etc. in “hard-core” philosophy communities, especially if these are part of the philosophy establishment as opposed to the social sciences one.

From the perspective of a broader understanding of philosophical realism, realist research in the Pawson, Tilley and RAMESES tradition has appropriated a name belonging to a much more varied set of conceptualisations and endeavours. The specificity of its understanding of concepts such as causation, mechanisms, theory and explanation, amongst others, while necessary and expected, can also cross into the parochial, contributing to a level of “realist group think” which outsiders to the intellectual community or even critical insiders may, at times, experience.

It is, however, an open question whether a methodological debate which is better embedded in a broader understanding of philosophical realism and/or more varied (realist) perspectives from the philosophy of science around causation, mechanisms, theories, etc. will change substantively, or even at all, the way the applied work is conducted.

1c. Realist synthesis in the context of other “alternative” synthesis methods

Realist reviews are one of a significant number of approaches developed in the 1990s / early 2000s in response to limitations of the mainstream, Cochrane type, systematic reviews.[22] These approaches seek to open up space for meaning-making, explanation, interpretation and theory; a broader understanding of evidence; a greater procedural flexibility; and opportunities for handling significant complexity in an endeavour that has become too self-limiting, largely by virtue of its narrow focus on evidence (or a focus on evidence, narrowly understood).

Basic bibliometric searches in PubMed covering the last five years suggest that out of 29 methodological alternatives to the mainstream systematic review and/or a narrative summary/ synthesis,[22] realist synthesis is amongst the four most widely used methods, alongside thematic synthesis, content synthesis and qualitative meta-synthesis (372 papers retrieved by “realist review” OR “realist synthesis”, Sep 2020).

Main advantages of the realist approach we perceived relative to pertinent alternatives were:

1) its focus on programmes as a key unit of analysis (with many interventions in palliative and end of life care in primary care and the community taking such a form);
2) the disciplined, “obligatory” way in which contextual influences are traced, through every CMO-configuration formulated (with outcome patterns in palliative and end of life care characterised by dramatic variations across contexts);
3) its openness to an exceptionally broad variety of evidence (accommodating the endless variety of perspectives that can be taken towards death and dying outside of palliative and end of life care);
4) its commitment to broad stakeholder involvement, including policy makers, practitioners, programme participants and the public, which acknowledges the value of each perspective, the privileged status of some perspectives relative to some questions but, at the same time, does not ascribe ultimate authority to any stakeholder group.
Table 1: Some strengths and weaknesses of a realist review from the perspective of an exemplar (Cochrane-type) systematic review

This table outlines key differences between a realist review and an exemplar (Cochrane-type) systematic review in terms of the research question, inclusion and exclusion criteria, and approach to literature searching. It is not an exhaustive comparison of the methods but, rather, focuses on challenges raised by initial reviewers of this paper. The last column summarises the steps we have taken to “bridge the gap”, i.e. improve on features of the realist review which are likely to be perceived as limitations or even failures in comparison to a mainstream systematic review. The steps taken are relatively unusual in the realist synthesis literature but, we argue, consistent with the spirit and methodological injunctions of the approach.

<table>
<thead>
<tr>
<th>Key element of a review</th>
<th>The realist approach</th>
<th>Strengths relative to the traditional (Cochrane-type) systematic review</th>
<th>Weaknesses from the perspective of the traditional systematic review</th>
<th>Strategy used in this review to bridge the gap</th>
</tr>
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<tbody>
<tr>
<td>Research question/ review focus</td>
<td>The initial research question can be quite broad, as it is typically generated by real-life practical concerns and policy needs as opposed to arising in a research context. It also tends to concern complex social programmes rather than discrete treatments such as new drugs. The review focus tends to become narrower as the study progresses.</td>
<td>The review questions asked are closer to the actual questions asked in complex policy and practice contexts. The work on focusing the review is highly responsive to new cues in the data, which could not have been anticipated at the start of the study.</td>
<td>The initial review questions may appear unspecific, possibly challenged as unanswerable in a scientific way. The process of focusing the review may appear to be changing what the review set out to achieve and, as such, to be compromising the integrity of the study.</td>
<td>We used a robust stepwise approach, involving 12 key stages, of making the transitions from the original to the final review questions. We still provided a high-level answer to some of the original review questions through the working typology of programmes in palliative and end of life care in primary care and the community.</td>
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2 The process of focusing the review involved the following stages described in the paper: 1. developing a realist typology of programmes for palliative and end of life care; 2. identifying a key theme within the typology which met five criteria (see paper for criteria). The time and timing theme was decided upon as a tentative focus; 3. test coding for CMO configurations on time and timing; 4. extensive team discussion. The other main candidate theme for a narrower review focus was “carers”. The focus on identification within the time and timing theme was decided upon through the following steps: 6. We identified themes related to time and timing in palliative and end of life care using all papers in the main dataset; 7. coded influential UK policy documents on palliative and end of life care for themes related to time and timing; 8. identified the intersections between themes in the research literature and themes in the policy documents (four key themes); 9. developed CMO configurations for all four themes; 10. conducted targeted searches on two of the themes and developed further CMO configurations based on them; 11. consulted stakeholders (the professionals’ Advisory Group and the PPI Group) on the emergent findings. 12. finalised the review focus on timely identification of the dying phase and timely initiation of palliative and end of life care services.

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<td>Research question/review focus, cont.</td>
<td>progresses and initial programme theories begin to be tested against the evidence retrieved (as opposed to being strictly set at protocol stage). 1 The review focus is decided upon iteratively, taking into account emerging explanatory possibilities and responding to feasibility demands as explanatory detail grows.</td>
<td>The strong explanatory aspect of a realist review, systematically supported by data, allows programme developers, practitioners and policy makers to make sense of patterns they know from experience and discern new ones. In turn, they can devise or refine programmes on the basis of “theories” (theories of change, logic models, lines of argumentation, etc.) as opposed to being confronted by piecemeal evidence which rarely speaks for itself.</td>
<td>Inclusion/exclusion criteria can appear vague. Explanations may be brought in from other areas creating a potential sense of confusion about the scope of the study. As typical inclusion/exclusion criteria such as health condition, setting, age group, etc. correspond to factors which may or may not play a role in theoretical explanations, fundamental features of the review, such as its target</td>
<td>Provided a detailed analysis table (Appendix 5) to demonstrate the logic of the derivations. Provided conceptual detail and numerical data on the 9 “levels of relevance” into which we classified studies (Appendix 4 on Literature searching).</td>
</tr>
<tr>
<td>Inclusion/exclusion criteria</td>
<td>Studies or parts of studies are included in the review depending on the degree to which they illuminate an emerging theory.</td>
<td></td>
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</table>


<table>
<thead>
<tr>
<th>Key element of a review</th>
<th>The realist approach</th>
<th>Strengths relative to the traditional (Cochrane-type) systematic review</th>
<th>Weaknesses from the perspective of the traditional systematic review</th>
<th>Strategy used in this review to bridge the gap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion/ exclusion criteria, cont.</td>
<td></td>
<td></td>
<td>population, setting, even overall topic, may seem to shift. Searches that deliberately (with good justification) reach outside the programme under study (and thus create a worse version of the limitations above) are considered a feature of an excellent review within the realist approach.³</td>
<td></td>
</tr>
<tr>
<td>Search strategy</td>
<td>Aims to identify sources rich in explanatory detail and evidence that can confirm or reject emerging hypotheses rather than the totality of relevant evidence. Develops iteratively, with targeted searches decided upon as the emerging theory is fleshed out.</td>
<td>Responsive to growing understanding of the topic of interest.</td>
<td>As the explanations at the lower levels may include concepts different to those in the review questions, the searches may appear insufficiently matched to the review questions.</td>
<td>Transparency about the search strategy and indication of the topics of all targeted searches, even if, ultimately, not used (Appendix 4 on Literature searching).</td>
</tr>
</tbody>
</table>


Appendix 2: Diagrammatic representation of rough programme theories, as developed at the outset of the study

Accompanies: Petrova, Wong, Kuhn, Wellwood and Barclay, “Dying and time”

Programmes, initiatives, tools, activities ...

EoLC patient identification approaches and tools
- “Surprise question”
- Structured prediction tools (examples?)
- GSF register

Approaches and tools for eliciting and recording care preferences (in the context of sensitive conversations) and developing a care plan around them
- GSF
- PPC (Preferred Priorities for Care)
- EPaCCS (Electronic Palliative Care Coordination Systems)
- service-specific care planning tools
- legalistic approaches and tools (e.g. ADRT, power of attorney)

Training
- In having sensitive/difficult conversations
- Recognising signs of dying
- Using the structured tools

Incentives
- E.g. QOF for GSF register, CQUINS, 1% and 2% LES and DES

Supportive context

Greater overall investment in and attention to end of life care

Local and national incentives for identifying EoLC patients, discussing their care preferences and preparing care plans

More open social conversation on death and dying

Underpinning assumptions/mechanisms:

As ~70% of deaths are predictable, timely identification is possible for the majority of patients. It needs to be enabled by the appropriate and consistent provision of awareness raising activities, training and tools.

High quality end of life care meets a patient’s individual preferences. These need to be identified through sensitive conversations, and adequately recorded and updated.

Lack of skills and confidence amongst health professionals in discussing death and dying is a main barrier. Improving training provision is key.

Progress with the identification and management of cancer patients has been significant. We need to focus on other conditions and also address other sources of inequality.
Appendix 2: Diagrammatic representation of rough programme theories, as developed at the outset of the study
Accompanies: Petrova, Wong, Kuhn, Wellwood and Barclay, “Dying and time”

Countervailing mechanisms

Prognosis is not that straightforward
- The disease trajectory for conditions other than cancer is far less predictable
- Research evidence suggests that predictions in End of Life Care (EoLC) are frequently inaccurate (e.g. White et al. 2016 systematic review)

Sharing a negative prognosis is not value-neutral – the value of maintaining hope may clash with values around truth (which is uncertainly anyway), preparation, freedom of choice and control over one’s life (and death)

Preferences are not fixed – patient preferences are not necessarily well shaped, can be dynamic, change on the basis of services available, etc.

Elicitation of preferences is complex
Having sensitive EoLC conversations cannot be taught in a 2-hour training session

This is not a conversation that fits in a 10-min appointment

Trust and the quality of the relationship with a patient are important. You need to have/ build the right relationship to have the conversation.

There is much noise in communication channels in principle, let alone in the case of conversations about death and dying, where euphemisms are often used (i.e. what clinicians have said and what patients have heard can be quite different)

Care planning
Ultimately, you are trying to predict something that is highly unpredictable.

If the services are not available, what you have planned for is totally irrelevant. It is even unethical as it may sound like a promise/ commitment when discussed with patients.

The identification of EoLC patients, the elicitation and recording of their preferences and the preparation of a care plan are more complex than may appear at first sight

Challenging contexts

Service level
If the services are not available, their availability unpredictable and we are going to do what we are going to do anyway, it is problematic, even unethical to be eliciting preferences.

Patient social context
Patient and his/ her family preferences may differ, and family members are also our patients. We need to consider them too in our planning.

Informational context
Data sharing only happens in pockets, not at all, or using traditional methods of inter-professional communication. We may be identifying and recording preferences and plans in our service, but if colleagues are not aware, much of that effort is wasted.
Appendix 2: Diagrammatic representation of rough programme theories, as developed at the outset of the study

Accompanies: Petrova, Wong, Kuhn, Wellwood and Barclay, “Dying and time”

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**Programmes, initiatives, services, etc.**
(in addition to standard practice, e.g. GP and DN visits, care provided by the family)

**Home-based services:**
- Community palliative care teams
- Hospice@home services
- Rapid response teams
- Paid carers
- Lay volunteers

**Provision of equipment for home care**

**Admission avoidance/ hospital stay reduction schemes:**
- Better information provision to ambulance staff and A&E through data sharing initiatives
- Fast track discharge
- Palliative care teams which work across the hospital and community
- Training

**Support for carers**
- Respite
- Training
- Counselling, confidential telephone lines, carer groups, etc.

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**Supportive context**

Greater investment in community services in general and community EoLC services in particular

Improvements in the local IT infrastructure (e.g. mobile working, data sharing)

Compassionate communities

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**Underlying assumptions/ mechanisms**

Home is the place where people feel most at peace, supported, safe and where they will be closest, in their final hours, to the ones who love them.

Community care is cheaper than hospital care.

Busy, open and impersonal hospital spaces can be a traumatic environment to die in and/or witness your loved one die.

If a patient prefers to be cared for at home (and this information is known and shared appropriately) and if we provide sufficient support at home, hospital admissions at the end of life are, generally, both unwanted and unnecessary.

There is a growing range of high quality community EoLC services. However, we need to address gaps in provision and sources of inequality.
Appendix 2: Diagrammatic representation of rough programme theories, as developed at the outset of the study
Accompanies: Petrova, Wong, Kuhn, Wellwood and Barclay, “Dying and time”

Countervailing mechanisms

There is a level of idealisation of home as a place of care/ death – e.g. help is not available at the press of a button and pain may be poorly controlled as services are not sufficient; the equipment turns the home into a hospital at home, etc.

Admissions may only appear inappropriate, even if a patient’s core preference is to be cared for/ die at home and even if those preferences are known – e.g. patients and family get scared; carers are exhausted; community services to keep the patient at home are not available at the time they are needed and it is safest to take the patient to hospital

Cost savings do not mean no investment

Good community services cost money, and this often needs to be invested in advance.

There is limited evidence on the overall costs of community services.

Family time is often unaccounted for, and the costs which are thus shifted to families can be significant.

Providing services which meet the complex and dynamic patient preferences and the highest standards of EoLC in the community is fraught with difficulty. The financial advantages of community care are not as definitive as they may seem.

Challenging contexts

Service level

The services which are part of standard practice (e.g. GP and DN involvement) are under so much pressure that an important pillar of community services is not as reliable as assumed.

The provision of EoLC community services is unequal.

Financial context

Funding cuts

Funding arrangements can lead to perverse incentives or disincentives to community care.

Geography

Remote, rural and disadvantaged areas will typically have less community services in place.

Areas which fall at administrative/ team coverage boundaries can fall between two chairs.

Social context

Community EoLC services rely on some level of support from a person’s social network. Not everybody has that.
Appendix 3: Stakeholder involvement

Here we report on the stakeholder involvement in our review using the Short Form of GRIPP2 (Guidance for Reporting Involvement of Patients and the Public) reporting checklist, while adding the Definition and Theoretical underpinnings parameters from the Long Form. Clarification of terminology and background assumptions was needed, as stakeholder involvement in realist research is broader than Patient and Public Involvement (PPI).

GRIPP2 forms as in:


1. Definition

While we did not start from a formal definition of stakeholder involvement, we had extensive team discussions of how to proceed with it and how to optimise it, particularly relative to standard challenges faced by PPI, such as professionalisation or unrepresentativeness of PPI groups. Below is a post-factum articulation of our starting positions:

Stakeholder involvement is a process whereby non-researchers and non-study participants are consulted with the goal of improving the study relevance; focus; applicability; chances of successful recruitment and retention of participants (or, in a review, the identification of relevant sources); valid analysis; and effective dissemination of findings. It is also a form of ensuring greater accountability and broader social feedback for research, which can become too disconnected from its intended users and beneficiaries and the society which often funds it.

More broadly, from the perspective of social inclusion and justice, the patient and public involvement aspect of stakeholder involvement is one of numerous ways in which individuals and social groups which are not in powerful positions can be encouraged to influence social conversations and practices which affect them; develop/refine the knowledge and skills to enable them to do so successfully; and develop the confidence that their views are valuable and that there are ways for them to be heard.

At the start of the work, our main concerns about PPI involvement were:

1) the tendency for PPI groups to be insufficiently representative of the breadth and substrata within ‘patients and the public’ and to reproduce entrenched social inequalities (e.g. PPI members are often white, middle class, educated, articulate, retired);
2) the tendency for PPI group members to become professionalised (and, arguably, lose some of the novice’s and outsider’s ability to notice and challenge problems and inefficiencies);

3) the degree to which PPI is being advanced as a requirement and unquestionable good in health research (provided it is “done well”, and not in a “tokenistic” way), limiting researchers’ abilities to engage probingly and critically with it without being accused of elitism and paternalism. While being strong supporters of PPI, we do believe the practice needs a far more open and critical debate to which we are aiming to contribute.

In responding to reporting requirements throughout the study (including in using the GRIPP checklists here, which address PPI involvement), we had to manage an ambiguity characteristic of realist methods and other methods relying on broad stakeholder engagement and involvement.

“Stakeholders” in such contexts includes not only patients and the public, but also professionals, policy makers, commissioners, etc. Moreover, no type of stakeholder in a realist study is, by default, privileged or more important than any other type of stakeholder. Different types of stakeholders are likely to have experience with, be sensitive to and ‘see’ different aspects of the big picture needed for the study.

Furthermore, as the involvement of professional stakeholders in research is typically structured around the needs of the study and the culture of research as opposed to the practices, rules, norms, etc. constituting a professional role (e.g. a health professional is a professional but outside of their field of practice), a professional stakeholder can also provide input ‘simply’ as a patient and member of the public.

It is an interesting and, we believe, open question if patients and the public should be the ‘privileged’ stakeholders (as having a reporting checklist only for this stakeholder group seems to imply). The question is particularly relevant in the case of research whose recommendations can be acted on first and foremost by health professionals, policy makers, commissioners, service developers, etc., even if its ultimate beneficiaries are intended to be patients and the broader society.

2. Theoretical underpinnings

Our literature review was conducted within a realist framework, as described in sources such as Pawson and Tilley (1997), Pawson (2002 a,b), Wong et al. (2013) and The RAMESES Project (2014). In realist studies, stakeholders with knowledge of a programme (intervention) are involved in ways that enable a researcher to put to test, and as a result confirm, falsify and refine, a theory about the programme’s workings. Expertise (and inexpertise) concerning a programme theory varies from aspect to aspect of a problem and from one programme to another (Pawson and Tilley, 1997; p.159-160).

Tentatively, it can be expected that programme subjects (e.g. patients in a healthcare context) will be more sensitized to the mechanisms in operation within a programme rather than to its contextual...
constraints and outcome patterns (op. cit., p. 160). As mechanisms, within a realist framework, provide reasons and resources encouraging participants to change, patients are well positioned to comment whether this has been effective, albeit most likely presenting a rather personal view of the interaction between programme mechanisms and their (the patient’s) pre-existing capacities (ibid.). Practitioners, in turn, are likely to have specific ideas on the aspects of the programme that make it work; likely to have experienced both successes and failures of it; and to have some awareness of people and places for whom and in which the programme works (op. cit., p. 161). Typically, they have a limited ability to systematise, abstract and generalise from their personal and institutional experience (ibid.).

Evaluators (researchers) are bringing in the theoretical knowledge – CMO-configurations they are familiar with from other programmes and more abstract propositions from social science theories. They are, however, stronger on form than content (op. cit., p. 161).

Each of these stakeholders has something to teach the others and something to learn from them (op. cit., p. 161).

Describing the role of stakeholders in realist studies, as per core methodological texts, is a research question in its own right. In our still evolving understanding, the realist approach does not ascribe a privileged status to patients and the public in comparison to other stakeholders in the research process. In contrast, mainstream PPI thinking, one of whose checklists we are using, appears to adopt such a view.

3. Aims

Relative to the theoretical underpinnings described above, stakeholders are involved in a realist study so as to contribute, with their experience and perspective, to the testing and refinement of a programme theory, which is the study’s main focus and outcome.

4. Methods

4.1. Convening stakeholder groups

Within the core study team, we had several (4-5) extensive discussions about stakeholder involvement and the most effective ways of enabling it.

The Cambridge Palliative and End of Life Care (CPEOLC) Group, which hosted the study, has a long-standing tradition of PPI involvement. However, as key concerns raised in the team discussions had been the downsides of PPI professionalisation and the value of broadening the variety of perspectives we had access to, we decided against approaching the PPI network of the CPEOLC group.

Initially, we engaged with an existing Sustainability and Transformation Partnership (STP) End of Life Care Board, which also has PPI representation, as a form of Advisory Group for the review. This was because all key local (Cambridgeshire & Peterborough) stakeholders in palliative and end of life care...
were already represented there. The original meeting provided us with some useful insights, but we decided to convene a project-specific Advisory Group.

We further approached a pre-existing PPI group, part of an infrastructure established and maintained by the National Institute for Health Research (NIHR) Cambridge Biomedical Research Centre (BRC). Unlike our CPEOLC network of PPI contributors, PPI members on this panel had no specific prior involvement in end of life care research. We assumed this would allow us to tap into less familiar points of view. 8 panel members attended the first meeting (early stages of the review) and 6 the second (towards the end of the review).

We also convened a project-specific Advisory Group using SB’s networks of palliative and end of life care professionals. 16 people expressed interest to join the group, of whom 8 were able to attend the first project meeting and 6 the second meeting. Several group members who could not attend either meeting provided feedback over email.

4.2. Activities

The main mode of engagement with the two stakeholder groups were face-to-face meetings, separate with each group: one meeting with each of the groups in October 2018 and one meeting with each of the groups in November 2019. The main goals of the first set of meetings were to discuss the scope of the review and the emerging rough programme theory. The main goals of the second set of meetings were to receive feedback and solicit reflections on key findings, serving to test further and help us refine the CMO-configurations under development.

Two members of the core research team attended each of the meetings (MP with either SB or IW) with the exception of the second PPI meeting (MP only).

Following the first meeting, we produced a 20-page document that brought together the input of the professionals’ Advisory Group and of the PPI Group. The document covered issues discussed at our original meetings and elicited initial Context-Mechanism-Outcome configurations. We circulated it to both groups with a request for feedback on “missing pieces”, if any, and “priorities within the priorities”. Feedback and additions were minimal, with overall comments that this was an impressive document.

Throughout the project and primarily around meetings with the groups, MP also had email exchanges with stakeholders, enabling further insight into the palliative end of life care-related experiences of patients, carers and health professionals and the workings of current services and programmes.

5. Outcomes of stakeholder involvement

5.1. Impact on the scope of the review

We received important guidance on the scope of the review from both groups. For instance, we were inclined to exclude research on care homes, hospices and day care centres. However, it
became apparent that such settings had been central to both positive and negative experiences of end of life care for members of the PPI Group while accompanying family members in their final days. The hospice representation on the professionals’ Advisory Group also meant the prominence of the setting remained high, while, within the team, we had discussed excluding literature on hospices by virtue of them being “too specialist”, even if community based.

Both meetings with the PPI Group underscored in emotional ways the importance of carers in palliative and end of life care. The research we had been identifying and screening, the policy documents reviewed, and the input of the professionals’ Advisory Group would not have resulted in a similar prominence of the carer perspective. The latter remained a key consideration throughout the data identification, analysis and synthesis stage, both in terms of explanatory models and issues prioritised.

5.2. Contribution to theory development and refinement

The discissions at the inaugural meetings with both groups, and particularly with the professionals’ Advisory Group, contributed significantly to developing the rough programme theory and specifying sub-questions within the broad review questions we had formulated for the study protocol. A detailed document on this contribution is available from the authors. Participant’s experiences, ideas and reflections from those meetings also supported the formulation of CMO-configurations during data analysis.

5.3. Impact on achieving balance

The second PPI meeting was exceptionally helpful in highlighting, in rather emotional ways at times, that a significant proportion of patients and carers do not receive palliative and end of life care at all. In view of their, at times, excruciating experiences, members of the PPI Panel intensely disagreed with some of our criticisms of a policy overemphasising identification of the end of life stage. The strong reaction against some of our evidence-based claims alerted us to the importance of careful framing and of fairness to the more conventional perspective, which should not be undermined, only expanded.

5.4. Impact on motivation and accountability

We experienced both forms of stakeholder involvement as very motivating in conducting the review. We felt encouraged to proceed with it and more confident in its importance and relevance.

We also had clear reminders that we need to give sufficient priority to the dissemination of findings and target dissemination efforts at a variety of primary audiences.

6. Discussion and conclusions

The involvement of both stakeholder groups was key to the direction of the study, as the specific outcomes above demonstrate.
7. Reflections/critical perspective

7.1. Representativeness and fluctuations of membership

Even though we sought an external PPI group (external to the Cambridge Palliative and End of Life Care research group) which could draw on a much larger pool of potential participants, the group was still insufficiently representative of the broader public.

It was also inconsistent in membership, with three new members and a new coordinator attending the second meeting. As a result, we needed to re-introduce the project and make space for the palliative and end of life care experiences that have brought each of the panel members (and us) to the meeting. Creating the right emotional environment is crucial for PPI involvement in palliative and end of life care research. However, in new groups or groups with significant fluctuations of membership, it may mean that the substantive work moves to the background for the better part of a meeting.

7.2. Expectations

In a literature review, the shape of the study is strongly determined by the available literature. There is a risk that the particularities of the available research, together with the need to focus the review further and further from its initial ambitions, creates, at the end of a study, the impression that the research team have taken very little of the contribution of stakeholders on board.

Our second PPI meeting also made us wonder if PPI groups are not almost exclusively consulted at the beginning of a study, making a meeting focusing on sense checking and refining findings unexpected and, by extension, requiring a much more detailed introduction. We found the meeting in question exceptionally helpful, yet in a diffuse way (see 5.3. Impact on achieving balance), almost unrelated to the specifics of our findings (which were discussed in much greater detail with the professionals’ Advisory Group). The findings moved to the background, as it felt far more important to open up space to discuss the issues that were coming up in the PPI Group there and then. Perhaps the Panel perceived their role as giving initial input on relevant issues, while the research team (represented by MP) was hoping to obtain feedback on highly specific and already formulated findings. Extra care may be needed in preparing and introducing such meetings, making clear they are “different” to normal PPI meetings.

7.3. Professionalisation – a revised perspective

A key challenge of PPI involvement we discussed at team meetings early on in the study was the level of professionalisation in PPI, including in the PPI Group associated with the Cambridge Palliative and End of Life Care Group – a group we had direct access to but decided not to approach for the purposes of this study. With the benefit of hindsight, we see many more of the advantages of such professionalisation. The iterativity of participation allows for the development of long-standing relationships between researchers and PPI representatives, and amongst the PPI representatives themselves. This, in turn, contributes to a safe, trusting environment which is key in palliative and...
end of life care research. Repeated participation also allows for the clarification of roles and expectations and for ongoing, both formal and informal, training in research methods.

We would like to thank sincerely all stakeholders who contributed to this study.

REFERENCES:

Appendix 4: Approach to searching and screening the literature

1. Generating the main dataset

The scope, databases and keywords for the literature searches were discussed from the start of the project, in the context of its regular team meetings, by IK (library and information specialist), MP (lead researcher, domain expert – palliative and end of life care), IW (systematic reviews expert), GW (realist methods expert and domain expert – general practice), SB (domain expert – palliative and end of life care and general practice). IK then designed test searches, whose contents and retrieval were reviewed by MP. Minor modifications were introduced. This work generated the main search strategy for the review. It combined four blocks of search terms around:

- palliative and end of life care;
- primary and community care;
- United Kingdom, using the filter for Medline by Ayiku et al.\(^1\) and adapting it for other databases;
- programme (theory, model, philosophy).

Eight databases were searched from 1990 onwards, with the search run on 24th April 2018:

- Medline via OVID
- Embase via OVID
- CINAHL via EbscoHost
- PsycINFO via EbscoHost
- Web of Science
- ASSIA via ProQuest
- Sociological Abstracts via ProQuest
- SCIE Social Care Online

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\(^1\) Ayiku L, Levay P, Hudson T, Craven J, Barrett E, Finnegan A, Adams R. The MEDLINE UK filter: development and validation of a geographic search filter to retrieve research about the UK from OVID MEDLINE. *Health Info Libr J*. DOI: 10.1111/hir.12187

The complete search strategy for each of the databases is presented at the end of this document, under **Main search, version 3**.

The main search generated a deduplicated dataset of **3039** citations.

Subsequently, records between 1990 and 1997 were removed after a decision to use the 2008 End of Life Care Strategy for England\(^2\) as a reference point and review publications 10 years before and 10 years after it. This decision aimed to ensure higher current relevance of the publications analysed and explore the impact of the Strategy on programme theories.

This resulted in a main dataset of **2,832** citations.

2. **Initial screening of the main dataset – refinement of inclusion-exclusion criteria; levels of relevance and saturation**

Relevance of a piece of evidence in the realist approach is determined relative to the programme theory being tested and refined. As the theory itself is under development – from the initial “rough” programme theory to the more refined realist programme theory which should be the outcome of the review – relevance is a dynamic and, at least initially, underspecified concept.

Inclusion and exclusion criteria thus cannot be decisively fixed during early stages of the review process or, if done, the explanatory potential of the review may be constrained. In the case of diverse and complex interventions, as was our case of programmes for palliative and end of life care in primary care and the community, the specification of definitive inclusion and exclusion is even more problematic.

Consequently, while we were guided by the set of inclusion-exclusion criteria outlined in the PROSPERO protocol (summarised in Box 1 below) and the rough programme theory developed within the team and consulted with stakeholders (Appendix 2), we still worked within relatively flexible boundaries of relevance, capable of accommodating the realist approach in the context of a highly complex topic.

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Box 1: Summary of inclusion-exclusion criteria as per PROSPERO protocol
https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=97218

**Age:** “Adults (over 18 years of age) whose death is perceived as imminent or who have advanced, progressive or incurable conditions. As realist reviews focus on theory development, we may, where relevant, consult literature on other populations, e.g. paediatric patients.”

**Interventions/ exposures:** “Programmes, interventions, initiatives, approaches, tools, etc. for the provision of palliative and end of life care in primary care and other community settings.”

Definition of end of life care referred to the last 12 months of life. Definition of palliative care (WHO) referred to physical, psychosocial and spiritual suffering. See details in full protocol.

Understanding of primary care and the community: mostly in opposition to hospital care and hospice inpatient care.

Examples of programmes of interest:
- the upskilling of General Practitioners and the support for optimising provision of palliative and end of life care in general practice (i.e. primary care-based programmes);
- care provided by palliative care specialists in the patients’ homes or as hospice outpatient services;
- initiatives aimed at improving end of life care in care homes;
- programmes which are developed, funded and staffed fully or primarily by charities and the voluntary sector;
- programmes offered by the private sector, e.g. paid-for care in patients’ homes;
- virtual community initiatives.

**Main outcomes:** 1) “good death”, typically as experienced by the family and carers of the deceased; 2) quality of care, as experienced by the patient, their family and carers, and healthcare staff, or as measured by quantitative metrics; 3) cost effectiveness.

**Additional outcomes:** coordination of care; reduction of unnecessary and unwanted hospital admissions; place of death.

**Study design:** No restrictions on study design. Non-empirical work also included.

Citations were first screened at the level of title, abstract and keywords by MP. The protocol envisaged that a second reviewer would screen 20% of all citations. Double screening in the context of systematic reviews with a strong interpretative component is typically seen as a way of enriching the analysis as opposed to enabling the checking for and correction of errors. In this review, we considered it a way of enhancing the process of theory development. As the team member who had started the double screening process left the institution, this work was not completed. Relative to the numerous other corrective and enriching processes established for the study (study team meetings; meetings of researchers conducting realist reviews across the Evidence Synthesis Working Group, etc...).
Group; meetings with a professionals’ Advisory Group and a Patient and Public Involvement Group; individual consultations with GW, the methodological expert on the study, etc.) and the openness to interpretative differences of any conceptual/theoretical review, we decided not to make alternative arrangements for double screening.

As opposed to aiming for a binary include-exclude decision, the process of screening was one of annotating citations for level of perceived relevance. Often, a brief note was added to the EndNote record to explain the decision, especially if it was not immediately clear from the paper title.

Inclusion categories:

- **Include, (potentially) core contents** – these citations were perceived as matching fully, or very closely, the questions of interest. In the majority of cases, they also fitted fully the main inclusion criteria (palliative and end of life care, community, UK, adults).

- **Include** – the generic ‘include’ category.

- **Include, broad** – for citations that covered topics outside of palliative and end of life care, community settings, adults and/or the UK, but suggested arguments and evidence that were relevant to the rough programme theory and its testing and refinement. Typically, the deviation from exemplary relevance was on 1 or 2 of the main inclusion criteria. If it was on more, the paper was more likely to be annotated as ‘maybe include’ (see below). That said, no numerical rule was followed around degrees of relevance.

Exclusion categories:

- **Exclude** – the generic ‘exclude’ category. The majority of directly excluded papers were from the basic sciences and from developing world healthcare systems (whose context we have pre-judged as too different to be sufficiently relevant).

- **Exclude, search precision-relevant** – we noticed that a number of terms (such as “C-terminal”, “N-terminal”, “carboxyl-terminal”, “terminal half-life”) reappeared frequently and consistently picked false positives, while never picking true positives. We started annotating such papers as an opportunity to explore strategies for improving the specificity of subsequent searches.

- **Exclude, unrecognised duplicate** – despite having conducted an automatic de-duplication of the dataset, duplicates were still appearing.
- **Exclude, yet broad relevance** – such papers had some relevance to issues of interest, but those issues were typically too broad features of the topic (e.g. overall tendencies in the distribution of staff across the health workforce).

- **Exclude, but preserve for bereavement review** – those papers addressed bereavement in primary care and the community, with the team commencing a realist review on complicated grief around the time of the screening. Under different circumstances, papers from this category would have been distributed across ‘exclude’ and ‘include’ categories. A small number of bereavement papers were included in this review too, but only to the extent to which they illuminated care before death.

### Uncertain categories

- **Maybe** – these were papers which 1) concerned settings, populations and geographies that fell under our exclusion criteria (e.g. hospital, children, non-UK), but some of the CMO configurations or elements they pointed towards appeared transferable; 2) had title/abstract/keywords which were not clear enough for a definitive decision; 3) discussed core ideas within the field of palliative and end of life care which could help elicit fundamental, but potentially too generic, CMO-configurations (as in papers on the history of palliative care); 4) explored highly specific settings and contexts of death and dying (e.g. prisons, suicides) which we were not excluding, but were not expecting to cover in detail either.

- **Include on limited information** – the title, abstract, and keywords suggested ‘include’, but there was a significant level of uncertainty to the decision due to limited information.

- **Exclude on limited information** – the title, abstract, and keywords did not give sufficient justification to follow up a paper to its full text, but there was a significant level of uncertainty to the decision due to limited information.

After screening 1,226 citations out of the main dataset (of 2,832), a level of saturation was achieved. Reaching saturation at this stage – roughly half of the dataset – was also taken as an opportunity to use half of the dataset for theory development (over and above that of the rough programme theory) and the other half for theory testing. The table below presents the proportions of the different levels of relevance of citations.
3. Targeted searches

Targeted searches – both simple and refined (the latter developed by IK, the library and information specialist on the project) – were run at various stages in the process of narrowing the review focus.

Main topics included:

- 24/7 specialist palliative care services
- night sitting, night nursing, care at night
- rapid response services
- referrals in palliative and end of life care
- staff shortages (in the NHS generally and palliative care more specifically), with implications for time available for patient care
- impact of performance management approaches (measurements, targets, incentives, etc.) on the work done (how “time is invested”)
- family size, structure and dynamics, and health of carers
- systematic reviews on prognosis in palliative and end of life care and/or predictions of survival or death.

Apart from the last topic (search strategy given at the end), all other topics were gradually excluded from the review focus. However, a number of the papers included in the review were found through those supplementary searches.
Main search, version 3

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1990 onwards

Searches run 24th April 2018

Medline

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid

MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

exp terminal care/ or exp palliative care/ or exp palliative medicine/ or exp terminally ill/ or exp hospices/ or ((end adj of adj life) or palliative* or terminal* or hospice*).ti,ab. or (last adj1 (week* or month* or day*)).ti,ab.

AND

(exp primary health care/ or exp community health services/ or exp home care services/ or exp general practice/ or exp family practice/ or exp charities/ or exp volunteers/ or exp organizations non-profit/ or exp community health nursing/ or exp spouses/ or exp home nursing/ or exp home care services/ or exp homes for the aged/) or

((Lay adj (care* or work*)) or volunteer* or (third adj sector) or (non-profit* or nonprofit*) or charit*
or spouse* or wife* or wives* or husband* or partner* or (home* adj2 (care or residential* or
nursing* or (old adj (folk* or person* or people*)))) or (primary adj (care or healthcare or (health adj
care)))) or (general adj practi*) or (family adj (practi* or doctor* or physician*)) or (community adj2
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(macmillan adj3 (nurs* or service* or support*)�)),ti,ab.

And

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or northern Ireland* or northern irish* or scotland* or Scottish* or ((wales or "south wales") not
"new south wales") or welsh).ti,ab,jw,in.)


And

(theor* or model* or concept* or philosoph* or program*).mp.

Embase
Embase 1974 to 2018 April 02

exp *terminal care/ or exp *palliative therapy/ or exp *terminally ill patient/ or exp *hospice/ or
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AND

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or exp social welfare/ or exp non profit organization/ or exp volunteer/ or exp community health
nursing/ or exp spouse/ or exp home care/ or exp nursing home/ or exp home for the aged/)

Or

((Lay adj (care* or work*)) or volunteer* or (third adj sector) or (non-profit* or nonprofit*) or charit*
or spouse* or wife* or wives* or husband* or partner* or (home* adj2 (care or residential* or
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(exp *united kingdom/ or (national health service* or nhs).ti,ab,in. or (gb or "g.b." or Britain* or (british* not "british Columbia") or uk or "u.k." or united kingdom* or (england not "new england") or northern ireland* or northern irish* or scotland* or Scottish* or ((wales or "south wales") not "new south wales") or welsh).ti,ab,jx,in.)

And

(theor* or model* or concept* or philosoph* or program*).mp.

Web of Science

TOPIC: (theor* or model* or concept* or philosoph* or program*)

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Timespan=All years

TOPIC: (united kingdom or uk or gb or great britain or england or scotland or northern ireland or wales or welsh or scottish or northern irish or great britain or great british or NHS or "national health service")

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC

Timespan=All years

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Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC

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S2

S1 ((DE "TerE "Palliative Care")) OR (DE "Hospice")

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SCIE Social Care Online

palliative or hospice or terminal* or "end of life" or "last week" or "last day" or "last month"

and

primary care or general practice or general practitioner or community care* or home care or district nurse or marie curie or macmillan or charity or charities or volunteer or voluntary or nursing home or care home or home for the aged or residential care

and

theory or model or programme or program or concept or philosophy

Targeted search on systematic reviews on prognosis in palliative and end of life care and/or predictions of survival or death

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to January 27, 2020>

Search Strategy:

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3  (surprise* adj2 question).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (89)

4  1 and 2 and 3 (29)
5  (review* or systematic*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (3802284)
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7  from 6 keep 1-4 (4)
8  2 and 3 (40)
9  5 and 8 (6)
10  9 not 7 (2)
11  from 10 keep 2 (1)
12  1 and 2 and 5 (77630)
13  ((predict* or prognos*) and (survival or "end of life" or "imminent death") and (review* or systematic*)).ti,ab. (45573)
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15  14 not 9 (203)
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Revised Date: 07/2015
CINAHL, EBSCOhost

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Appendix 5: Further detail on programme types

Box 3, complete version: Types of palliative and end of life care programmes in primary care and the community in terms of broad programme logic expressed as CMO-configurations

Note: Here we offer a typology of palliative and end of life care programmes in primary care and the community in terms of the overarching, generic theory (taking the form of a CMO-configuration) to which they appear to subscribe. We have abstracted the high-level, generic CMOs from specific CMOs characterising the example programmes analysed, with the examples coming from the 253 “core contents” citations.

For instance, on the basis of the brief programme descriptions we have reviewed, we suggest that the abstract mechanism underpinning innovative discharge roles is the management of boundaries between services and settings. Similarly, we suggest that intermediate care beds can be thought of as a boundary management initiative – both between service types (hospital and community) and patient needs (requiring intense professional input and oversight – requiring more limited professional input and oversight). Thus, two programmes which may “look” very different belong, in our classification, to the same type by virtue of their shared theoretical underpinning – shared programme logic of mechanisms causing their outcomes. Much further work is required to elicit the theories behind the specific programmes included here and to test our choices of a “defining theory”.

Appendix 5 to Petrova, Wong, Kuhn, Wellwood & Barclay, “Dying and Time”, Mar 2021
Type 1 programmes: Programmes seeking to improve the availability of services where systemic and critical gaps exist: in terms of time, location, intensity and responsiveness (when, where, how much and how quick)

When palliative care is needed in time periods outside of normal working hours and in underserved areas (C), end of life care outcomes will improve dramatically and efficiently (O) only if services are time-of-the-day-independent (M), adapted to the location where they are offered (M), flexible (M) and responsive (M).

Examples of Type 1 programmes that address time and timing
- 24/7 services
  - Out of hours (OOH) services
    - OOH specialist palliative and end of life care services
    - OOH pharmacy provision of drugs
    - OOH generalist services
    - “Informal” OOH services (e.g. GP providing personal phone number)
  - “Twilight” services (in the underserved periods between daytime and OOH services)
  - Night services
    - Night nursing
    - Night sitting
  - Hospice day care services
  - Rapid response services

Examples of Type 1 programmes that address location, coverage and proximity
- Home-based services, including Hospice at Home
- Hospice outpatient services
- GP practice palliative and end of life care clinics
- Community centres services
- Host family respite
- Rural services
- Telecare services
- Deprived areas services
- (relative) Services moving closer to the users

Examples of Type 1 programmes that address intensity and responsiveness
- Rapid response services
- Improved standard practice (new types of prioritisation)

Type 2 programmes: Programmes defined through the broad aspect of our humanity and needs being addressed, often as forms of care and support provided by a particular professional or lay group

As suffering and pain are multimodal (C), we can achieve better quality of life for dying patients (O) when we acknowledge the numerous modalities of experiencing pain and suffering and by acting in (more) holistic ways (M).

Subtypes of Type 2 programmes in terms of the form of therapy or support offered

Alternative and complementary therapies
- Arts and art therapy
- Basic body comfort
  - Hands-on enablement
  - Equipment-enabled comfort
- Basic human presence and support – being with, staying with; bridging the “dying world” and the “world outside”; small, intangible acts of kindness
- Beauty and wellness
- Clinical and medical care
- Financial support and advice
- Hands-on care
- Holistic care
- Movement, exercise, physiotherapy
- Nature, gardens, the outdoors
- Personal care support
- Psychological support and counselling
- Rehabilitation
- Respite
  - Day care respite
  - Host family respite
  - In-home respite
  - Institutional respite
  - Video respite
- Social support
  - Opportunities for meeting people
  - Social activities
  - Social environment as created by volunteers
  - Social support from fellow patients

BMJ Support Palliat Care 2021;0:1–15. doi: 10.1136/bmjspcare-2021-003066
Type 3 programmes: Programmes addressing the management of boundaries and transitions

As the needs of dying patients at transition points can be extra complex (C) and different services often lack sufficient levels of integration and coordination (C), we can enable each patient to receive the most appropriate and timely care within resource limits (O) if we manage service boundaries and transitions better, in rational yet person-centred ways (M).

Examples of Type 3 programmes that address discharge management
- Rapid hospital discharge to enable home death
- Discharge roles (e.g. Discharge Community Link Nurses)
- Discharge letters and templates
- Discharge policies and pathways
- Discharge practices when palliative care needs reduced or prognosis modified

Examples of Type 3 programmes that address referral management
- Clarification of referral criteria (triggers) and development of documentation
- Rules on referral initiators – who can refer?
- Rules on referral timing – when to refer?
- Referral triggers – what needs to happen so as to refer?
- Referral audits for quality improvement

Examples of Type 3 programmes that address “midway solutions” between service types
- Intermediate care beds
- Community hospitals
- Hospice at Home services
- Primary care doctors with visiting rights to local hospitals

Examples of Type 3 programmes that address the management of transitions and working across settings
- “Alignment models”, e.g. aligning the work of GPs and care homes
- Bridging roles – liaison roles, secondments, dual roles
- Case reviews across settings
- Electronic data sharing, Electronic Palliative Care Coordination Systems (EPaCCS)
- Hand-over protocols and forms, particularly for OOH
- Multidisciplinary team meetings
- Service integration work
- Transportation across settings
- Partnerships between ambulance service and other settings

Type 4 programmes: Programmes prioritising patient-centredness, ownership and empowerment

As patients and their carers have a range of diverging end of life care needs, preferences and wishes (C), we are far more likely to achieve the goals of care that truly matter to them (O) if these are clearly elicited, recorded and acted upon (M) and, more broadly, if services are co-developed with patients and carers (M).

Subtypes of Type 4 programmes with examples

Programmes centred around tools for eliciting and recording patient preferences and wishes for end of life care
- Preferences elicitation and care planning tools – e.g. Preferred Priorities of Care, EPaCCS, ReSPECT
- Legally binding tools – e.g. Advanced Directives to Refuse Treatment (ADRT)
- Design of new tools
- Training and support for the use of existing tools
- Broader initiatives for increasing the uptake of such tools

Programmes based on shared decision-making innovations
- Patient-led case conferences

Programmes based on support for self-management

Programmes for co-developing services with patients

Peer support programmes
- Peer education programmes for older people about Advance Care Planning

Programmes for community-based discussions of end of life care

Appendix 5 to Petrova, Wong, Kuhn, Wellwood & Barclay, “Dying and Time”, Mar 2021
### Type 5 programmes: Programmes addressing different phases of an illness or of the dying process

As the phase in the trajectory of an illness and/or the proximity to death of a patient has a profound impact on their treatments and care needs (C), we can improve outcomes for patients and support the sustainability of the health service (O) by structuring and delivering services in a phase-centric way which enables their optimisation, with no relevant needs missed and no unnecessary activities undertaken (M).

**Subtypes of Type 5 programmes (perhaps more often presenting as service structures and pathways than new programmes)**

- Services around the delivery of a terminal diagnosis
- Services during active treatment
- Services after discharge
- Services at recurrence/exacerbation
- Services in the final weeks and days of life
- Anticipatory bereavement
- Bereavement support

### Type 6 programmes: Programmes taking a systemic approach

As the terminal phase of an illness or the process of dying can be very complex and fast changing and involve a large number of services (C), we are more likely to achieve positive outcomes for the patients, their family and the system (O) and less likely to encounter crisis situations (O) if terminal illness and/or the process of dying is approached in a systematic, proactive and anticipatory manner rather than a piecemeal and reactive one (M).

**Subtypes of Type 6 programmes with examples**

- Programmes aiming to improve identification of patients in need of palliative and/or end of life care
  - Development of new prediction and risk stratification tools
  - Broader, more systematic implementation of prediction and risk stratification tools
  - Improving staff abilities in identifying patients at the end of life
  - Improving the skills of junior and lower level staff in communicating concerns about patients higher up the hierarchy
  - Appropriate recording and communication of such information to other services, e.g. through Registers (EPaCCS)

- Programmes enabling discussions of death, dying and care at the end of life

- Programmes aiming to improve Advance Care Planning (ACP)
  - Tools, proformas, templates
  - Enhancing basic staff skills in using them
  - More in-depth training on using ACP tools, acknowledging challenges such as differences between family and patient preferences, dynamics of preferences, service limitations, creating the right environment for the conversations, etc.
  - Initiatives to support the broader, more systematic use of such tools

- Programmes aiming to improve integration of care and handling diffusions of responsibility
  - Case management initiatives
  - Key worker initiatives
  - Data sharing for improved informational continuity
  - Palliative care coordination centres
  - Bridging roles

- Programmes aiming to develop or refine existing protocols and pathways

- Programmes based on the use of decision-making tools

- Programmes aiming to improve monitoring and evaluation systems and processes
  - Enhanced annual reviews of patients
  - Patient recall systems and processes
  - Palliative and end of life care registers and dashboards
  - Provision of (comparative) data on palliative and end of life care processes and outcomes

- Programmes facilitating internal change through external support
  - Peer facilitation for practices
  - Educational facilitation

- Programmes creating a broad supportive environment
  - Financial incentives
  - National guidance
  - Local change management initiatives
  - Identifying and supporting ‘champions’

“Meta-programmes” – highly systematic ways of developing new local initiatives and programmes

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*Appendix 5 to Petrova, Wong, Kuhn, Wellwood & Barclay, “Dying and Time”, Mar 2021*
Type 7 programmes: Programmes seeking improvements through staff and volunteer development

When work environments value palliative and end of life care training and development as part of their business-as-usual rather than a matter of short-term projects (C), palliative and end of life care provision across the board improves (O) through investment in the knowledge, skills, motivation, attitudes, etc. of professionals and lay persons providing care (M) and through creating effective role structures and arrangements (M).

Subtypes of programmes and examples

Programmes based on developing new staff roles and forms of task distribution
- Extended nurse prescribing in palliative care
- Peer facilitators with 'dual roles' (e.g. GPs with special interest in PEoLC)
- Bridging roles

Programmes for staff training and support
- From palliative care specialists to generalist staff
- Training in specific skills
  - Communication
  - Palliative and end of life care prescribing
  - Advance Care Planning
- etc.
- Training for specific staff groups
- Training by using different approaches, contexts and platforms (hands-on, online, on-the-job, etc.)
- Support for generalist staff, or even specialist staff, in dealing with rare diseases

Programmes expanding the roles of volunteers and community members
- Compassionate cities initiatives
- Volunteers in hospices
- Death dealers

Type 8 programmes?: Programmes defined through the support they provide to informal carers?

The presence of carer-focused programmes in the research literature, as sampled, was not on a par with the presence of programmes of the other seven types. Further research is needed on the degree to which support for informal carers in palliative and end of life care translates into programmes which are defined in terms of their carer-focused mechanisms rather than including them as a secondary component.
Appendix 6: CMO-configurations and supporting evidence on the identification of patients at the end of life, short-term prognosis and associated referrals

The Appendix has 3 parts:

- Excerpts from UK policy documents and reports concerning the identification of end of life care (EoLC) patients
- Supplementary Table 1: Context-Mechanism-Outcome configurations around identification, prognosis and referrals based on them
- Supplementary Table 2: Abstract-level scoping of most recent (last 5 years) systematic reviews on prognosis

1. Excerpts from UK policy documents and reports concerning the identification of end of life care (EoLC) patients

The list of excerpts is illustrative. The documents chosen were considered as highly likely to have had significant impact on palliative and end of life care services and practice in England, by virtue of being prepared by broad coalitions of UK palliative and end of life care organisations; the UK Government/Department of Health and Social Care; the UK Parliament; and NICE, the National Institute for Health and Care Excellence (a non-departmental public body of the UK Department of Health and Social Care), which provides national guidance and advice to improve health and social care.1,2 The excerpts are also illustrative for each of the documents. We have selected 2-7 claims per source which represent its position and which were, ideally, succinct and focused on identification and prognosis only.

Even if far from exhaustive, we believe the list gives a sufficiently reliable overview of the mainstream position around patient identification in current UK palliative and end of life care policy and practice. We have also made sure to include caveat statements (around the challenges of identification and uncertainty at the end of life), even if they are not too prominent in a document. They are indicated by (uncertainty) preceding a statement. Our arguments criticising the mainstream view concern the lack of sufficient recognition of the challenges of prognosis and identification rather than a complete lack of it. However, this lack of balance, we claim, leads to a range of important unintended negative consequences.

The documents are arranged in chronological order. Statements are direct quotes (indicated by italics; or if the document quotes a contributor, by italics and inverted commas, with the source added). Minimal connecting or clarifying statements have been added by us (normal font).

Q followed by a number (e.g. Q7) is a unique identifier for quotes referred to in the table of Context-Mechanism-Outcome configurations further below.

1 https://en.wikipedia.org/wiki/National_Institute_for_Health_and_Care_Excellence
2 https://www.nice.org.uk/about
Q 1. The [EoLC] care pathway involves the following steps:
- Identification of people approaching the end of life and initiating discussions about preferences for end of life care;

[6 further steps follow] (p. 9-10)

Q 2. Many health and social care staff have had insufficient training in identifying those who are approaching the end of life, in communicating with them or in delivering optimal care. To address this, a major workforce development initiative is now needed, with particular emphasis on staff for whom end of life care is only one aspect of their work. (p. 12)

Q 3. (uncertainty) The definition of the beginning of end of life care is variable according to individual person and professional perspectives. (p. 47)

Q 4. The major challenges in relation to the delivery of high quality end of life care in the community include:
- Poor identification, assessment and coordination of end of life care within some general practices;

[6 further challenges follow] (p. 84)

Q 5. (uncertainty) It is difficult, if not impossible, to calculate the cost of end of life care in this country. This is partly because of the difficulty in defining exactly when end of life care starts. (p. 150)

1 Department of Health. End of Life Care Strategy (Jul 2008)

House of Commons Health Committee report (Mar 2015)\(^4\)

Q 6. The situation is unlikely to improve unless clinicians feel confident to identify people who may be near the end of life and to start conversations with their patients about their wishes. (p. 3, Summary)

Q 7. “The NHS continues to struggle to properly identify people who are in the last stages of life, unless they have a terminal or otherwise life-threatening condition … This in turn means people are not able to plan properly or encouraged to discuss decisions about their future care … A failure to understand multi-morbidity and frailty and the trajectory of people’s health living with either (or often both) means the NHS is not agile, failing to allow care and support to switch tracks quickly when someone is approaching the end of life.” (from Age UK written evidence to inquiry; p. 14)

Q 8. The Sue Ryder Care Centre for the Study of Supportive, Palliative and End of Life Care has also found that staff caring for frail and seriously ill older people have difficulty recognising the point at which a transition to a palliative care approach may be appropriate. (p. 14-15)

Q 9. Many of those who provided written evidence to this inquiry expressed the opinion that health care staff need support to develop their competence in identifying, providing care to and communicating with people at the end of life and their families and carers. (p. 20)

Q 10. “Our case work has shown that there is a need to communicate in a way that is both sensitive but also makes clear the prognosis and what options there are for care based on the outcomes individuals may want for themselves.” (evidence provided by the Parliamentary and Health Service Ombudsman; p. 20)

Q 11. “When patients are not informed about their prognosis and are not asked about their care and medical treatment preferences, they are denied the right to participate in decisions and might not have the death they want.” (evidence provided by Compassion in Dying; p. 21)

Q 12. Witnesses to the inquiry expressed concern that there is a lack of research evidence to inform the development of models for early identification of those people who would benefit from receiving palliative care and how to deliver palliative and end of life care services to non-cancer patients. (p. 39)

Q 13. (uncertainty acknowledged; then largely overridden) We know that much about recognising dying and impending death is uncertain and challenging. However, timely identification and honesty where there is uncertainty is key to the quality of care – all else follows. (p. 18)

Q 14. Effective systems for person centred care need to encompass: systematic ways of reaching people who are approaching the end of life, effective assessment as well as effective decision making support, care coordination, care planning, and care delivery. (p. 19)

Q 15. Good care is also about identifying people approaching the end of life earlier so that there is time and opportunity to prepare, discuss and plan care, and time to put that care in place to meet people’s individual needs and preferences. (p. 19)

Q 16. (uncertainty) The AMBER care bundle is a simple approach used in hospitals when there is clinical uncertainty of recovery. The approach supports staff, patients and families who wish to continue with treatment in the hope of a recovery, while encouraging open conversation about people’s wishes and preferences should things get worse rather than better. (p. 21)

Q 17. All CCGs should also be clear about the efficiency gains to be made when people are able to make plans and express preferences early about their care so that unnecessary hospital admissions are avoided. We know that people’s experiences of care are better and services more coordinated and efficient when clinical staff can identify people’s needs earlier and share and implement end of life care plans more easily. (p. 25-26)

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National Institute for Health and Care Excellence guideline for service delivery (Oct 2019)

Q 18. (uncertainty) End of life care includes the care and support given in the final weeks and months of life, and the planning and preparation for this. For some conditions, this could be months or years. (p. 35)

Q 19. First recommendation in Guideline is about: 1.1 Identifying adults who may be approaching the end of their life, their carers and other people important to them. (p. 7)

Q 20. People managing and delivering services should develop systems to identify adults who are likely to be approaching the end of their life (for example, using tools such as the Gold Standards Framework, the Amber Care Bundle or the Supportive and Palliative Care Indicators Tool [SPICT]). This will enable health and social care practitioners to start discussions about advance care planning, provide the care needed, and to support people’s preferences for where they would like to be cared for and die. (p. 7)

Q 21. (uncertainty acknowledged; then largely overridden) Although the evidence was limited, the committee agreed that identifying adults who may be approaching the end of their life supports health and social care practitioners to start discussions about advance care planning. This should ensure that the person near the end of life is provided with the support that they may need now or later to help them stay where they would like to be cared for and die. It also gives them time to consider and re-evaluate their needs with their health and social care practitioners. (p. 22)

Q 22. The committee wanted to emphasise the importance of identifying people systematically. There are already some systems in use for identifying people approaching the end of their life, which are given as examples in the recommendations. However, there were no studies comparing and evaluating their effectiveness in service delivery so the committee could not recommend a particular system. (p. 22)

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2. Supplementary Table 1: Context-Mechanism-Outcome configurations around identification, prognosis and referrals based on them

The row below is illustrative to help explain the structure of the table and the abbreviations and symbols used in it, presented in the notes that follow.

<table>
<thead>
<tr>
<th>Parameter type and identifier</th>
<th>Context-Mechanism-Outcome (CMO) configurations or elements</th>
<th>Sources</th>
<th>Key pieces of evidence, theoretical claims and interpretations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PROGNOSIS, TIMELY IDENTIFICATION</strong></td>
<td></td>
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<tr>
<td><strong>1.1.</strong></td>
<td>Timely identification of end of life stage as enabling preparation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A, C, M, O</td>
<td>The identification of patients who are likely to be in the last year of their lives (A/O intermediate)</td>
<td>Sims-Gould et al. 2010&lt;br&gt;Steinhauser et al. (trigger)</td>
<td>(A, M, O) Identification enables preparation which, in turn, enables meeting an individual's needs and preferences and achieving a good death</td>
</tr>
<tr>
<td>Original programme theory</td>
<td>allows sufficient time for discussing, planning, organising and coordinating care around a patient's needs, wishes and preferences (M), for instance around their preferred place of care (O); their family's needs and capacity (M/C); the availability of local services (C); and in view of the sustainability of the health system (C).</td>
<td>Core policy documents (see pp. 2-5 above)&lt;br&gt;Roikjær et al. 2019 *** BROADER (hospital)</td>
<td>Programme theory 'seed' statements</td>
</tr>
<tr>
<td></td>
<td>In terms of broader life (C), such identification allows ... [continues below]</td>
<td>Domain knowledge of team</td>
<td>Department of Health, 2016. The Government Response to the Review of Choice in End of Life Care</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>“Good care is also about identifying people approaching the end of life earlier so that there is time and opportunity to prepare, discuss and plan care, and time to put that care in place to meet people’s individual needs and preferences.” (p. 19)</td>
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<td>National Institute for Health and Care Excellence guideline for service delivery, 2019</td>
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<td></td>
<td>“People managing and delivering services should develop systems to identify adults who are likely to be approaching the end of their life ... [continues below]</td>
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</tbody>
</table>
**Context-Mechanism-Outcome (CMO) configurations or elements**

The CMOs presented in the table can be complete configurations, partial ones (e.g. M-O, C-O) or, occasionally, individual elements (C, M, O). If only the latter, they have been included because they appear to have significant explanatory potential, but either cannot be weaved in a complete CMOs yet or can contribute to many (typically the C-element). At times, A, for programme activity, is also added to make the explanations clearer and better connected to ‘visible’ features of a programme. Longer CMO-configurations are introduced by a brief heading, which can be based on any of the elements.

**CMO colour coding**

- **Green** CMOs or elements are the ones intended and (partly) articulated by the original programme theory. The versions offered in the table are refinements of the rough programme theory.
- **Black** indicates that particular negative CMO configurations are recognised by the original programme theory. In fact, the latter is often developed as an attempt to address them.
- **Red** indicates CMO configurations which are not, or only minimally, recognised by the original programme theory but limit its applicability. In such configurations, M is a countervailing mechanism, C is a context blocking the functioning of the programme theory mechanisms, and O is a resulting outcome.
- **Yellow** is for CMO configurations or elements which are consistent with the original programme theory but are mentioned only minimally and remain mostly tacit.

**Abbreviations**

The following are non-standard conceptual subtypes and notations (non-standard in the realist method) we have been experimenting with for additional accuracy of attributions:

- **A** – programme activity
- **A** fail – used to indicate a failure to perform a programme activity
- **O** multiple – sets of outcomes which tend to co-occur
- **O** intermediate – indicates outcomes that are elements of a chain of steps and dependencies which may lead to primary outcomes. Primary outcomes may be patient-relevant, carer-relevant, health professionals-relevant and health system-relevant.
M/O, C/M or other combinations – when an element can perform more than one formal function, depending on the perspective.

Symbols differentiating reference types (sources column)

**Asterisks** indicate a process of literature searching and identification other than the core search (no asterisk means the reference is from the core search):

* indicates references from a focused, targeted search – searches conducted with the goal of further specifying and testing the theories under development (search strategies in the Literature searching appendix);

** indicates references obtained through citation tracking – following up on work referenced in the papers we have been analysing or using forward citation tracking (looking up papers which cite the one being reviewed);

*** indicates a reference from the pre-existing collections of the authors, recommendations from colleagues or serendipitously identified papers.

**BROADER** indicates that the source did not fall fully within the scope of the review in terms of its theme (palliative and end of life care), geography (England, potentially UK) and population (adults). Using such broader resources is entirely in line with the realist approach and, in fact, an expression of its exploratory logic. The particular “deviation” from an exemplary source is shown in brackets:

- BROADER (country – e.g. Australia)
- BROADER (domain – e.g. mental health)
- BROADER (population – e.g. children).

Sims-Gould et al. 2010 (trigger) – i.e. smaller font sources followed by “(trigger)” were the first sources to prompt us to code an issue, but the latter was a relatively marginal point in them. Typically, we have sought further sources to refine the CMO-configurations of interest and to substantiate them with evidence/ theoretical claims.

The realist approach relies heavily on the so called “nuggets of evidence”. One way to describe them is as minor, peripheral claims or data in a source document, which, however, provide a pertinent confirmation/ refutation of a hypothesis from the realist study. The awareness of the value of nuggets of evidence meant that, especially early on, we have been coding minor mentions of issues because of their relevance rather than richness and depth.

Furthermore, most primary care and community interventions in palliative and end of life care are complex interventions, meaning they have many elements, many of which do not receive focused attention in a publication.

Finally, publications in any research field have a sufficiently shared discourse and background. Core ideas emerge quickly from any set of publications. Which came first is a matter of the approach to literature searching and the chronology of analysis. Also, any researcher familiar with the domain (and we are) can formulate a broad range of statements from its discourse provided a trigger.

Such sources are included for transparency and to support explorations of the potential impact on the review outcomes of the literature searching approach and chronology of reading/coding.

**Domain knowledge of team** – occasionally, this has been added to the source column. Some CMO-configurations were refined or expanded through the background knowledge of the domain experts on the team (SB and MP for PEOLC and SB and GW for general practice). If a statement appears in the CMO-configuration without a corresponding evidence in the last column, then it was based on such broader domain knowledge. This has only been done for claims we consider uncontroversial, “givens” in the field of (UK) palliative and end of life care, and which, precisely because of being taken for granted by insiders, are not always made explicit.

**Key pieces of evidence, theoretical claims and interpretations**

If the evidence, theoretical claims and interpretations in the last column are coming from an empirical study and from its own data (rather than its background literature review, for instance), we have included a brief description of its (Setting/ Participants) and (Methods).

To help readers evaluate the credibility of the evidence and its relevance to their own work. If the authors’ description is not transparent enough of important study limitations, we add further critical comments and caveats to the brief Methods description. These setting/participants and methods overviews have been developed in a holistic way, e.g. without the use of a systematic checklist to assess or include parameters.
When the supporting statements added to this column are not empirical evidence or if, while based on evidence, make a significant leap from it (as in the discussion section of a paper, for instance), we have added an indication:

- Programme theory ‘seed’ statements – for excerpts from policy documents or reports we have used as a ‘seed’ to grow a rough programme theory. They are relevant evidence in the sense of serving to demonstrate the validity of our rough programme theory. They are often based on some evidence, but this is rarely made explicit in the statement.
- Explanation for pattern of data – typically offered by the authors of a paper. It is based on evidence but makes a theoretical leap from it.
- Framing sections evidence/statement – evidence or statements which come from the background (introduction) or discussion of a paper. As they are presented briefly, they often lack detail and indications of the trustworthiness of the original source.
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<td><strong>A, C, M, O</strong></td>
<td>The identification of patients who are likely to be in the last year of their lives (A/O intermediate) allows sufficient time for discussing, planning, organising and coordinating care around a patient’s needs, wishes and preferences (M), for instance around their preferred place of care (O); their family’s needs and capacity (M/C); the availability of local services (C); and in view of the sustainability of the health system (C). In broader life, outside of the contexts of healthcare (C), such identification allows both patients and carers to prepare for death and develop a level of acceptance of it (M/O), such as through putting their affairs in order (M/O), making the best of the time they have got left (M/O), completing what has been left undone or finding better closure for it (M/O), settling and healing relationships (M/O), expressing love, regret, forgiveness, gratitude, appreciation ... (M),</td>
<td>Department of Health, 2016. The Government Response to the Review of Choice in End of Life Care “Good care is also about identifying people approaching the end of life earlier so that there is time and opportunity to prepare, discuss and plan care, and time to put that care in place to meet people’s individual needs and preferences.” (p. 19) National Institute for Health and Care Excellence guideline for service delivery, 2019 “People managing and delivering services should develop systems to identify adults who are likely to be approaching the end of their life (for example, using tools such as the Gold Standards Framework, the Amber Care Bundle or the Supportive and Palliative Care Indicators Tool [SPICT]). This will enable health and social care practitioners to start discussions about advance care planning, provide the care needed, and to support people’s preferences for where they would like to be cared for and die.” (p. 7)</td>
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</tbody>
</table>
reminiscing about their life (M) and finding a sense of value and meaning in it (M/O), and leaving a legacy for future generations (M/O).

Identification of the end of life stage (A) is thus crucial for enabling the best possible outcomes for the patient, their family and other people important to them, and for the sustainability of the health system (e.g. by avoiding unnecessary admissions and interventions) (O multiple).

See also the policy quotes on pages 2-5, in particular Q7, Q11, Q17 and Q21.

(M, O) Having time to prepare for death and reflect on one’s life seen as aspects of a good death by patients and carers

Sims-Gould et al. 2010

“Steinhauser et al. (5) studied the perspectives of patients and their families on a good death and found that it would include: completion (adequate time to prepare for death); pain and symptom management; clear decision making; affirmation of the whole person; the opportunity to reflect on one’s own personal accomplishments and time to be with others.”

(M, O intermediate) Positive non-medical ways of preparing for death and positive experiences/ outcomes that may result from them

Roikjær et al. 2019

“The interventions [using personal narratives in palliative care] were all relatively brief psychotherapy based on reminiscence theory in which patients re-evaluate past experiences with the intention of resolving and integrating past conflicts, bringing new significance and meaning to their life and empirical work on either dignity or end-of-life experience.”

“The framework underlying dignity therapy and legacy building was the model of dignity, which focuses on dignity-conserving tasks such as settling relationships, sharing words of love and preparing legacies of memory and shared values.”

“[The] outlook model has tasks very similar to the dignity model although they name them development tasks: sense of completion in
relationships with family, expressions of regret and forgiveness, acceptance of gratitude and appreciation and sense of meaning of one’s life.”

“All interventions have the sense of meaning as a core concept. Furthermore, all interventions share the underlying assumption that these tasks can be facilitated through the personal narrative with components of life review, forgiveness and legacy and positively affect the outcomes of quality of life, psychosocial and existential distress.”

<table>
<thead>
<tr>
<th>1.2.</th>
<th>Dangers of delayed identification of the end of life stage</th>
<th>Mintzer and Zagrabbe 2007 * BROADER (United States) (trigger)</th>
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</thead>
<tbody>
<tr>
<td>A, C, M, O</td>
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<td><strong>(A, M, O) Lack of timely identification and/or communication of prognosis deprives patients of choice at the end of life and may lead to a bad death</strong></td>
<td><strong>(A, M, O) Lack of timely identification and/or communication of prognosis creates hard-to-manage uncertainty for families and other people close to the dying person and deprives them of choices they should have had</strong></td>
</tr>
<tr>
<td>Functional equivalent of 1.1, negative framing</td>
<td><strong>Dangers of delayed identification of the end of life stage</strong></td>
<td><strong>Programme theory ‘seed’ statement</strong></td>
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<td></td>
<td><strong>Delayed identification of the end of life stage (A fail /O intermediate)</strong> may mean that patients, families and other people close to them, as well as health professionals, do not have time to prepare for the death (M).</td>
<td><strong>House of Commons Health Committee report, 2015</strong></td>
<td><strong>Department of Health. End of Life Care Strategy, 2008</strong></td>
</tr>
<tr>
<td></td>
<td>Patients may then feel robbed of time they believed they had (M/O), be denied the opportunity to have a choice in how they die (M/O), experience severe distress (O) and, ultimately, not have the death they wanted (O).</td>
<td><strong>“When patients are not informed about their prognosis and are not asked about their care and medical treatment preferences, they are denied the right to participate in decisions and might not have the death they want.” (p. 21; evidence provided by Compassion in Dying)</strong></td>
<td><strong>“Although not directly told, Keith’s wife suspected that his life was limited. As a result she was unsure about contacting her four children.”</strong></td>
</tr>
<tr>
<td></td>
<td>In the context of overburdened services (C) and lack of awareness of a patient’s preferences (M), health professionals may not make the best decisions (M), even when trying to do their best (M/C) and, for instance, undertake unnecessary interventions (M/O) or not be able to arrange the right services in time (M/O). This may result in suboptimal care; bad, even horrible, deaths; sense of guilt and frustration for the</td>
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| health professionals; unnecessary costs and litigation for the health system (O <sup>multiple</sup>). Families and other people close to the patient may also feel robbed of time and choice they feel they should have had (M/O), go through avoidable distress and traumatic experiences around the time of death (O) and be left to deal with feelings such as guilt and complicated grief for years to come (O). | She also struggled with the decision about informing Keith’s priest, as she did not want to alarm her husband but at the same time she knew he would wish to see a priest. She also felt upset and cheated that she had not been able to say goodbye to her husband before he was re-ventilated.” (p. 25)  

House of Commons Health Committee report, 2015  

“The decisions made by healthcare professionals about a patient’s care are often made with the best intentions and to try to ensure the highest care quality. However, in cases where decisions are made without the opportunity for the patient and their family to have their preferences assessed fairly, the patient ends up feeling distressed by their lack of choice, and that they have received a poor service.” (p. 24; evidence provided by The Parliamentary and Health Service Ombudsman)  

(A, M, O) Lack of timely identification leads to delayed referrals to specialist care. As a result, patients cannot be provided with optimal support. This is also frustrating for PEoLC practitioners.  

Framing sections evidence/ statement  

Mintzer and Zagrabbe 2007  

“Often, hospice is called in very late, within the last week or two of life—sometimes the last day or two—when optimal support and preparation for death cannot be provided. Such late referrals are frustrating to practitioners who deal with end-of-life care.” |
<table>
<thead>
<tr>
<th>1.3.</th>
<th>Limitations of knowledge, skills and information as a core reason for delayed identification</th>
</tr>
</thead>
<tbody>
<tr>
<td>A, C, M, O</td>
<td>Delays and omissions in identifying patients who may be approaching the end of their lives (A ( \text{tail/O intermediate} )) are often a matter of insufficient training in palliative and end of life care (M), insufficient experience (M), insufficient knowledge of/ information about a particular patient shared by other colleagues within the health system (M). They are also more likely in diseases other than cancer (C), as their disease trajectories are less predictable (M).</td>
</tr>
<tr>
<td>[A/O, M] Failures of identification often result from the lack of knowledge, skills and training of staff</td>
<td></td>
</tr>
<tr>
<td>Department of Health 2008</td>
<td>Programme theory ‘seed’ statements</td>
</tr>
<tr>
<td>Domain knowledge of team</td>
<td>[M]any health and social care staff have had insufficient training in identifying those who are approaching the end of life, in communicating with them or in delivering optimal care. To address this, a major workforce development initiative is now needed, with particular emphasis on staff for whom end of life care is only one aspect of their work. (p. 12)</td>
</tr>
<tr>
<td></td>
<td>House of Commons Health Committee report, 2015</td>
</tr>
<tr>
<td></td>
<td>“Many of those who provided written evidence to this inquiry expressed the opinion that health care staff need support to develop their competence in identifying, providing care to and communicating with people at the end of life and their families and carers.” (p. 20)</td>
</tr>
<tr>
<td></td>
<td>See also the policy quotes on pages 2-5, in particular Q6 and Q8.</td>
</tr>
</tbody>
</table>

(A/O, M, C) Identification of end of life stage is much easier in cancer and, respectively, challenges of identification are more likely in other conditions |

Programme theory ‘seed’ statements |

Department of Health. End of Life Care Strategy, 2008 |

“3.3 Some people with long term conditions remain in reasonably good health until shortly before their death, with a steep decline in...
the last few weeks or months of life. Others will experience a more gradual decline, interspersed with episodes of acute ill health from which they may, or may not, recover. A third group are very frail for months or years before death, with a steady progressive decline.

3.4 These three patterns, or trajectories, are illustrated in Figure 1 [Note, the review team – not shown here]. Some authors have suggested that the first pattern may be typical of cancer, the second may be typical for people with organ failure (e.g. those with heart failure or chronic obstructive pulmonary disease), and the third may be typical for people with dementia.

3.5 However, empirical evidence from a cohort of patients who died of a variety of conditions over a two year period indicates that the picture is more complex (Figure 2).” (pp. 45-7)

“...the trajectories of different conditions do, however, vary. The predictability of prognosis towards the end of life is generally somewhat greater for cancer than for other conditions.” (p. 97)

House of Commons Health Committee report, 2015

“The British Medical Journal has described three distinct illness trajectories for people with progressive chronic illnesses:
• a trajectory with steady progression and usually a clear terminal phase; mostly cancer
• a trajectory with gradual decline, punctuated by episodes of acute deterioration and some recovery, with more sudden, seemingly unexpected death; for example, respiratory and heart failure
• and a trajectory with prolonged gradual decline; typical of frail elderly people or people with dementia.” (p. 13)

Note, the review team: The BMJ paper referred above is the paper mentioned in the EoLC strategy (Murray S et al. 2008). This time,
however, the added complexity indicated by the Strategy (which then points to Figure 2, representing much more complex data provided by M Gott) has been lost.

“They [British Heart Foundation] note that GPs admit that introducing palliative care is fairly straightforward for people with cancer, who typically have a clear terminal decline, but much more difficult for patients with other life-threatening illnesses.” (p. 15)

**1.4. A, C, M, O**

*Timely identification works better in theory than in practice*

<table>
<thead>
<tr>
<th>Prognostic judgements in end of life care (A) – the foundation for triggering end of life specific courses of action and services (M) – are made through various combinations (M) of probabilistic objective criteria (M), professional judgement (M), and/or subjective intuitions (M) using a variety of prediction modalities and frameworks (A, M) by health professionals of different professional backgrounds (C), of different levels of skills and experience (C), in different phases of an illness or frailty (C) with different degree of input from other professionals (C) and relative to dynamic patient presentations (C), resulting in problematic prognostic accuracy (O).</th>
</tr>
</thead>
<tbody>
<tr>
<td>White et al. 2016 ***</td>
</tr>
<tr>
<td>White et al. 2017 ***</td>
</tr>
<tr>
<td>Downar et al 2017 ***</td>
</tr>
<tr>
<td>Bluhm et al. 2016 **</td>
</tr>
<tr>
<td>McGaughey J 2017 *</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>White et al. 2016</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(Setting/ participants) Palliative populations and settings; “real patients” rather than hypothetical cases; English language papers.</strong></td>
</tr>
<tr>
<td><strong>(Methods) Systematic review of 42 studies on predictions of survival in palliative patients, over 12,000 prognostic estimates. Databases: MEDLINE, Embase, CINAHL, and the Cochrane Database of Systematic Reviews and Trials from inception to 2015. Papers assessed for bias (QUIPS tool) but not excluded on the basis of it.</strong></td>
</tr>
<tr>
<td>Distribution of percentages of accuracy for categorical survival estimates (re-organisation of data from Fig 2 of White et al., original presentation by type of categories)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>% accuracy CI Estimates Categories Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>&lt; 30%</strong></td>
</tr>
<tr>
<td>23.3%</td>
</tr>
<tr>
<td>27.2%</td>
</tr>
<tr>
<td>27.3%</td>
</tr>
<tr>
<td>27.6%</td>
</tr>
<tr>
<td><strong>30%-39%</strong></td>
</tr>
</tbody>
</table>
Such challenges around the accuracy of prognosis are further exacerbated by emotional factors (M), such as reluctance to share bad news (M); perceptions of a preference, on the part of patients, to maintain hope (M); or some health professionals’ own resistance to “admitting failure” in not being able to do more for a patient (M).

<table>
<thead>
<tr>
<th>Percentage Range</th>
<th>Proportion</th>
<th>Confidence Interval</th>
<th>Sample Size</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-36%</td>
<td>30.2%</td>
<td>24.6-36.4</td>
<td>248</td>
<td>Shah 2006</td>
</tr>
<tr>
<td></td>
<td>31.7%</td>
<td>21.9-42.9</td>
<td>82</td>
<td>Stiel 2010</td>
</tr>
<tr>
<td></td>
<td>31.9%</td>
<td>22.7-42.3</td>
<td>94</td>
<td>Bruera 1992</td>
</tr>
<tr>
<td></td>
<td>32.0%</td>
<td>19.5-46.7</td>
<td>50</td>
<td>Kao 2011</td>
</tr>
<tr>
<td></td>
<td>33.3%</td>
<td>29.4-37.3</td>
<td>580</td>
<td>Gripp 2007</td>
</tr>
<tr>
<td></td>
<td>34.0%</td>
<td>31.8-36.2</td>
<td>1835</td>
<td>Hui 2011</td>
</tr>
<tr>
<td>40-49%</td>
<td>41.0%</td>
<td>35.1-47.1</td>
<td>273</td>
<td>Zibelman 2014</td>
</tr>
<tr>
<td></td>
<td>45.0%</td>
<td>35.0-55.3</td>
<td>100</td>
<td>Glare 2004</td>
</tr>
<tr>
<td>50-59%</td>
<td>51.5%</td>
<td>44.9-58.1</td>
<td>233</td>
<td>Vigano 1999</td>
</tr>
<tr>
<td></td>
<td>55.6%</td>
<td>38.1-72.1</td>
<td>36</td>
<td>Selby 2011</td>
</tr>
<tr>
<td></td>
<td>55.8%</td>
<td>51.3-60.1</td>
<td>511</td>
<td>Brandt 2006</td>
</tr>
<tr>
<td></td>
<td>56.7%</td>
<td>49.5-63.6</td>
<td>203</td>
<td>Muers 1996</td>
</tr>
<tr>
<td></td>
<td>57.4%</td>
<td>54.3-60.6</td>
<td>987</td>
<td>Gwilliam 2013</td>
</tr>
<tr>
<td></td>
<td>57.6%</td>
<td>52.7-62.3</td>
<td>429</td>
<td>Fromme 2010</td>
</tr>
<tr>
<td>Over 60%</td>
<td>72.8%</td>
<td>66.9-78.2</td>
<td>254</td>
<td>Thomas 2009</td>
</tr>
<tr>
<td></td>
<td>78.4%</td>
<td>75.8-80.7</td>
<td>1128</td>
<td>Addington-Hall 1990</td>
</tr>
</tbody>
</table>

Downar J et al. 2017

(Setting/ participants) Patients with cancer (5 studies), renal failure (7), end-stage heart disease, end-stage lung disease, heterogenous population with critical illness, a primary care practice population (1 study each). Median incidence of death for the cohorts 15.1%.

(Methods) Systematic review of 16 studies/ 17 cohorts (11 621 patients) on the Surprise Question (“Would I be surprised if this patient died in the next 12 months?”). Death at 6 to 18 months the outcome of interest. Eleven databases/platforms searched. Overall risk of bias,
as per Quality in Prognosis Studies tool: high in 4 studies, moderate in 10 studies and low in 2 studies.

For death at 6 to 18 months, the pooled prognostic characteristics for the Surprise Question (SQ) were:

67.0% sensitivity (95% CI 55.7%–76.7%) – amongst those who died, those who were expected to die as per the Surprise Question;

80.2% specificity (73.3%–85.6%) – amongst those who survived, those who were expected to survive as per the Surprise Question;

37.1% positive predictive value (95% CI 30.2%–44.6%) – the proportion of patients who died when the clinician predicted dying;\(^8\)

93.1% negative predictive value (95% CI 91.0%–94.8%) – the proportion of patients who survived when the clinician predicted survival.

“The surprise question performs poorly to modestly as a predictive tool for death, with worse performance in noncancer illness.”

“Prognostic performance was worse for noncancer illness, missing more than one third of those who died and more than two-thirds of positive results proved to be false.”

“Based on these findings, the SQ should not be used as a stand-alone prognostic tool, and we do not know whether it is more accurate for identifying patients with unmet palliative needs than it is for those in the final year of life.”

\(^8\) Simple formulations of PPV and NVP taken from White et al. 2017

<table>
<thead>
<tr>
<th>White et al. 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(Setting/population)</strong> Patients with end-stage renal disease (8 studies), cancer (6), heart failure (4), sepsis (1), COPD (1) and variety of diagnoses (6). Patients died within the specified timeframe on 4217 occasions (16%). Country: 10 studies UK; 9 US; Germany, Hong Kong, India, Italy, Japan, New Zealand, Spain (one study each). English language publications only.</td>
</tr>
<tr>
<td><strong>(Methods)</strong> Systematic review of 26 papers on the Surprise Question, relevant data extracted from 22 papers. 25,718 estimates. Eight databases (no retrieval from one). Quality assessed with the Newcastle-Ottawa scale; papers not excluded but appraisals used in sensitivity analysis.</td>
</tr>
<tr>
<td>Wide variation in the reported accuracy of the SQ:</td>
</tr>
<tr>
<td>11.6% to 95.6% – range for <strong>sensitivity</strong></td>
</tr>
<tr>
<td>13.8% to 98.2% – range for <strong>specificity</strong></td>
</tr>
<tr>
<td>13.9% to 78.6% – range for <strong>positive predictive value</strong></td>
</tr>
<tr>
<td>61.3% to 99% – range for <strong>negative predictive value</strong></td>
</tr>
</tbody>
</table>

Note, the review team: The reviews of Downar et al. 2017 and White et al. 2017 on the surprise question appear to be targeting the same papers, although one frames the review around predicting death and the other around identifying end of life patients. There are more papers and predictions in the review of White et al. 2017. Further work is needed to assess the degree of overlap in their data sources, but both reviews identify suboptimal and also variable performance of the SQ.

Note, the review team: Sources of data which can be used to assess the accuracy of predictions at a very local level include:
- evaluations of anticipatory prescribing practices;
- data from Electronic Palliative Care Coordination Systems.
<table>
<thead>
<tr>
<th><strong>(C) Professional background, impact</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>White et al. 2016</td>
<td></td>
</tr>
<tr>
<td><em>See above for brief overview of methods and setting/ participants (first White et al. reference)</em></td>
<td></td>
</tr>
<tr>
<td>No consistent evidence that one professional group or sub-group of clinicians was any more accurate than any other profession or sub-group.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>(C) Experience, impact</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>White et al. 2016</td>
<td></td>
</tr>
<tr>
<td>Level of experience as improving accuracy – mixed evidence (confirmed in 2 studies, refuted 3).</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>(C) Multidisciplinary team working, impact</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>White et al. 2016</td>
<td></td>
</tr>
<tr>
<td>Accuracy may be better when the prognosis is made by a multidisciplinary team (2 studies).</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>(C) Proximity to death, impact</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>White et al. 2016</td>
<td></td>
</tr>
<tr>
<td>Time frame of the prognosis (e.g. imminent death vs. within 12 months) appeared to affect both the accuracy overall and the relative accuracy of different professionals (2 studies).</td>
<td></td>
</tr>
<tr>
<td>White et al. 2017</td>
<td></td>
</tr>
</tbody>
</table>
“The meta-regression indicated that the increase in time frame did not impact on the diagnostic accuracy of the SQ: comparing up to 30 days with 12 months (difference in accuracy = 0.8%, 95% CI –12.8 to 14.5, \( P = 0.901 \)) and comparing up to 6 months with 12 months (difference = 4.3%, 95% CI –10.8 to 19.4, \( P = 0.561 \)).”

**Professional background and proximity to death**

White et al. 2016

Nurses and healthcare assistants may be better at recognising imminent death than other professionals (2 studies).

**Type of estimate, impact**

White et al. 2016

Probabilistic estimates (4 papers) may be slightly more accurate than categorical or continuous temporal estimates of survival.

*For evidence on professionals’ emotions around sharing a negative prognosis (Bluhm et al. 2016), see 2.6.1. below.*

**Observations of patient condition made by low-level staff ignored by more senior staff**

Sims-Gould et al. 2010

BROADER (Canada)

Setting/ participants: Ontario, Canada, 110-bed long-term faith-based, not-for-profit care home; 18 deaths or residents with dementia in the previous year; experiences of dying and end of life care for patients with dementia of personal support workers and non-clinical workers. Personal support workers (PSWs, also called ‘care aides’).
needed for such judgements (M). Time pressures for more senior staff (C) exacerbate the tendency to ignore what appears unimportant/unreliable as information (M).

deliver the majority of hands-on resident care; non-clinical workers here include maintenance and support staff.

(Methods) Part of a broader study using “focused ethnography”. In this paper – data from 44 personal support workers (17 interviews and focus groups, unclear how many of which), and 4 non-clinical workers (4 interviews). Thematic analysis of data by three researchers, both independent work and team discussions. Findings presented to staff for validation.

“It is frustrating, and I know I’ve had an experience of people that are deteriorating really, really quickly, and [the nurses] are still telling you, ‘No, get them up, get them in the dining room,’ and you’re...in tears.”

“Yeah, you are just bottom of the barrel. What do you know about that person, you know? Even just day-to-day care, if you go and tell an RN something is different about somebody — ‘Oh, they were like that a month ago. That’s happened before.” (p. 127)

(C) Time constraints exacerbate the tendency

“Time constraints often fracture communication or create a feeling that one’s voice or perspective is not valid or valued by others.” (p. 127)

<table>
<thead>
<tr>
<th>1.6.</th>
<th>Awareness of long-standing needs and PEoLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>C, M, O</td>
<td>Some terminally ill patients (cancer diagnosis) (C), whose needs for symptom control and help with self-care have been relatively long-standing (C), may be less likely to receive input from community specialist palliative nurses in the last year of life (A/O), possibly</td>
</tr>
<tr>
<td>Addington-Hall and Altmann 2000</td>
<td>(C, O) Association between longer-standing health needs and provision of PEoLC care</td>
</tr>
<tr>
<td>Addington-Hall and Altmann 2000</td>
<td>(Setting/participants) England, 20 district health authorities (self-selected but nationally representative); community specialist palliative nurses (Macmillan, hospice at home, others); by now, old data (deaths in last quarter of 1990).</td>
</tr>
</tbody>
</table>
due to being perceived as chronic disease patients rather than PEoLC patients (M).

Early identification of terminal phase (A) may thus, paradoxically, be associated with reduced likelihood of being prioritised for community PEoLC (M/O).

**(Methods)** Random sampling of 270 deaths (through death certificates) per health district, though cancer deaths sampled disproportionately due to interest of health districts (54%); semi-structured interviews with bereaved carers about the last 12 months of life; 71% response rate for cancer deaths (2074/2915).

“Patients who had had symptoms for more than 6 months were less likely to receive care from these nurses”

In logistic regression, being dependent on others for help with self-care for more than 1 year (along with four variables representing types of cancer) was associated with a decreased likelihood of receiving community specialist palliative care.

**(M) Perception of patients as chronic disease rather than palliative**

Addington-Hall and Altmann 2000

Authors’ explanation of pattern of data

“Patients who had had symptoms for more than 6 months were less likely to receive care from these nurses, suggesting that these patients may have been seen as falling within the rubric of chronic disease care rather than palliative care.”

<table>
<thead>
<tr>
<th>1.7.</th>
<th>The uncertainty of predictions may be “reverse engineered” to secure better care for patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>C, M, O</td>
<td>Lucas et al. 2008 (M, O) Revising prognosis so that it fits referral criteria to enable a patient to receive enhanced services</td>
</tr>
<tr>
<td></td>
<td>Lucas et al. 2008</td>
</tr>
<tr>
<td></td>
<td>(Setting/ participants) Bradford, UK (large and deprived borough); hospice at home team covering 3 areas with a combined population of 386,000. Service targeted at patients with a prognosis of 6 weeks or</td>
</tr>
</tbody>
</table>
and refer a patient on the basis of a “reconsidered” (but, potentially, no less accurate) prognosis (M). Patients are thus enabled to access the services that would meet their needs (O), but which were out of bounds due to their prognosis-focused referral criteria (M).

less, irrespective of diagnosis. Practical nursing support, supplementing that provided by the patient's own nursing team. Team composition: 1 Sister, 2 Staff Nurses, 6 Marie Curie trained Health Care Assistants, and Agency staff. Service context of high staff turnover, considerable work pressure and absence of adequate admin support.

(Methods) Data collected from Jul 2001 (inception of service) to Jun 2006. Postal questionnaire used as part of clinical audit. Respondents: carers (N eligible = 570, n sample = 289, response rate 50.7%), district nurses (n = 508, 89% response rate, no reminders) and GP's (n = 444, 78%, no reminders). 15 questions for carers; 12 for DNs and 3 for GPs. Ample free-text comments, even if questionnaire did not afford it (e.g. extra pages added, written in margins). Qual data analysed using grounded theory techniques.

“Anecdotally, we identified that in some cases GPs were referring people with non-cancer diagnosis and claiming a prognosis of six weeks or less in order to give their patients access to the enhanced services hospice at home could offer. In effect the inexact science of prognosis is being used in two ways – one to exclude some people and one to include them in this sought after service even when GP’s may not have an evidence based judgement to reassure all parties that the six week prognosis was realistic. In effect the six week rule was manipulated to maximise care for individual patients.” (p. 11)
### TIMELY REFERRAL

to community PEoLC services, following or not from short prognosis/ identification of EoLC stage

<table>
<thead>
<tr>
<th>2.1. rough A, C, M, O A, C, M, O (functional equivalent, negative framing)</th>
<th>Benefits of timely (generally earlier) referral to palliative and end of life care services in the community</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timely referral to (community) PEoLC services (A) allows sufficient time for evaluating and organising care around (M) the patient and family needs, wishes, preferences and life circumstances, e.g. suitability of home for home care (M, C), and also relative to the capacity and timelines of local services (C). This enables the best possible outcomes for the patient, their family, and the sustainability of the health system (e.g. by avoiding unnecessary admissions and interventions). It also makes it more likely that the patient dies at home, if this has been their wish (O).</td>
<td></td>
</tr>
<tr>
<td>In contrast, late referrals (A) may preclude opportunities (M) for the adequate and comprehensive assessment of needs (M), eliciting a patient’s wishes and preferences (M), arranging care in view of the above (M), as well as for the patient, family and generalist staff to benefit from highly effective, fine-tuned, flexible decisions and courses of action (M) around reducing pain and suffering and increasing quality of life (O), enabled by</td>
<td></td>
</tr>
<tr>
<td>Fellowes et al. 2003 (trigger)</td>
<td>[A, O, C] Timely, which is generally earlier, referral improves outcomes for cancer patients, but is unclear if this is the case for non-cancer patients</td>
</tr>
<tr>
<td>Mintzer and Zagrabbe 2007</td>
<td>Programme theory ‘seed’ statement</td>
</tr>
<tr>
<td>BROADEN (United States) (trigger)</td>
<td>National Institute for Health and Care Excellence guideline for service delivery, 2019</td>
</tr>
<tr>
<td>National Institute for Health and Care Excellence 2019</td>
<td>“There is a body of research into the optimal timing of referral to specialist palliative care in cancer patients, which generally points to earlier referral leading to better patient-reported outcomes. The committee noted that similar evidence is very limited for patients with a non-cancer diagnosis, for example in patients with progressive organ failure, such as advanced heart failure, or patients with life-limiting neurological disease, such as motor neurone disease or dementia. Such patients are typically referred very late to specialist palliative care, if at all. Further research would compare outcomes for people having a combination of early identification and specialist palliative care input with those for people having usual care.” (p. 19)</td>
</tr>
<tr>
<td>Department of Health 2008</td>
<td>[A, O] Late referrals as a source of frustration for specialists</td>
</tr>
<tr>
<td>Domain knowledge of team</td>
<td>Framing sections evidence/ statement</td>
</tr>
<tr>
<td>Mintzer and Zagrabbe 2007</td>
<td></td>
</tr>
</tbody>
</table>

the greater knowledge, skills and experience of specialist staff (M/C).

This may mean that patients endure (long) periods of preventable pain and suffering, are more vulnerable to unnecessary admissions, and/or do not have their end of life care wishes met (O multiple).

Families and other informal carers may also not receive the support they need (M/O) and, as a result, struggle with providing care (M/O), experience significant deterioration of their own health and well-being (M/O), and not be able to cope with crises in home care (M), resulting in unnecessary hospital admissions (O). After the death, they may experience feelings of guilt and complicated grief (O) and, potentially, initiate complaints against the health services (O), which had let them down (M).

Late referrals (A fail) also result in frustration for palliative and end of life care professionals (O). This is because opportunities for providing optimal care have been missed (M). Also, with the often short timelines in end of life care and often limited capacity of PEoLC services (C), specialists have not been given the chance to respond in the ways they would have wanted or were expected of them (M). This can create/ contribute to interprofessional tensions and mistrust (O/M/C).

There is, however, uncertainty whether earlier referrals, which are generally associated with better patient-reported outcomes in cancer, are similarly recommended for patients with non-cancer conditions. (C)

“Often, hospice is called in very late, within the last week or two of life—sometimes the last day or two—when optimal support and preparation for death cannot be provided. Such late referrals are frustrating to practitioners who deal with end-of-life care.”

(A, O) Late or no referrals as a source of complaints against the health system

Department of Health. End of Life Care Strategy, 2008

“Its [of the Healthcare Commission] ‘Spotlight on Complaints’ report assessed just over a total of 16,000 complaints made about NHS organisations between July 2004 and July 2006. Approximately half of these related to care given in acute hospitals. Of these, no less than 54% related in some way to end of life care. In its latest report ‘Spotlight on Complaints 2’ (April 2008) the Commission examined 50 cases where the primary complaint was about end of life care. These complaints were mainly about poor communication, lack of basic comfort, privacy and psychological care and late or no referral for specialist palliative care. Relatives frequently commented that they seemed to be the first to recognise that the patient was dying. Inappropriate invasive procedures were often undertaken, even in the dying phase.” (pp. 24-25)

Note, the review team:

The rough theory we have described to the left includes formulations based on the background knowledge of the team which have not yet been linked to a sufficient number of illustrative sources (contents of this column). “Timely/ early vs. late referrals” at this high level of generality was de-prioritised as a potential focus for further targeted searches, as it was expected to follow a similar logic to that around timely/ early and delayed identification (1.1. and 1.2. above).
We thus focused the articulation of CMOs and associated evidence on more specific issues, as represented from 2.2. to 2.10. below.

<table>
<thead>
<tr>
<th>2.2.</th>
<th>Unclear referral criteria and/or limited awareness of them</th>
</tr>
</thead>
<tbody>
<tr>
<td>C, M, O</td>
<td>Even if generalist staff have sufficient awareness of local community PEoLC services and value them (M/C), their referral patterns may still be suboptimal (O) due to uncertainty about appropriate referral times and associated services (M).</td>
</tr>
</tbody>
</table>

*Hypothesis (M), this review: Perceptions of lack of clarity of a criterion/ set of criteria often relate to the need to interpret whether a particular case meets a criterion/ set of criteria or not. In this sense the problem may be in the grey area of whether something counts as meeting a criterion (as would be, for instance, “end of life stage”) rather than in the lack of clear articulation and communication of relevant criteria. The solution then is not so much in clarifying the referral criteria, but in exploring the potentially sizeable grey zones of non-exemplary cases.*

<table>
<thead>
<tr>
<th>Fellowes et al. 2003</th>
<th>(M) Uncertainty and confusion about appropriate referral times</th>
</tr>
</thead>
</table>

*Fellowes et al. 2003*  
*(Setting/ participants) UK, Marie Curie Nursing Service*  
*(Methods) Study-specific questionnaire to District Nurses in 37 community trusts (4 randomly selected, stratified for urban/ rural, per each of the 10 Marie Curie Nursing Service districts in the UK). Questionnaires sent randomly to 40 or all (if less) DNs within a participating trust. 879 out of 1,379 surveys (64% response rate). A significant number of missing responses to some questions, but also almost 250 DNs provided additional, free-text comments.*

*“The MCNS [Marie Curie Nursing Service] is valued, but confusion exists about appropriate referral times and the services provided.”*  
*Fellowes et al. 2003*  
*Framing sections evidence/ statement*  
*“However, the study also found that other health care professionals were uncertain about when they should refer people to the service. The study also found a perception within the MCNS that some referrals were inappropriate (Higginson and Wilkinson, 2002).”*  
*Note, the review team: We do not see direct evidence in Higginson and Wilkinson 2002 to justify the interpretation of Fellows et al. but leave their claim and our challenge for further critical assessment.*
### 2.3. Potential over-confidence in own knowledge of generalist staff

| M, O | Generalist staff may perceive their PEoLC knowledge and ability to deal optimally with dying patients as better than they are (M), resulting in fewer or later referrals to specialist services than beneficial for patients (O). |

| Fellowes et al. 2003 | (M) Potential discrepancy between actual and perceived PEoLC knowledge of a significant proportion of generalist staff |

Fellowes et al. 2003

**Setting/participants** UK, Marie Curie Nursing Service

**Methods, brief** Questionnaire completed by 879 District Nurses (64%).

See 2.2. for details

“It is surprising that almost 70 per cent of district nurses felt that they had sufficient expertise to provide adequate palliative care but only 13 per cent had attained a recognised palliative care qualification.”

Top reason for not referring: “able to give this patient appropriate palliative care myself”, selected “often” by 68.7% of respondents (820 responses to question).

### 2.3.1. Unintended consequences of brief PEoLC training events for generalist staff?

| A, M, O (tentative hypothesis) | Brief PEoLC training events for generalist staff (A) may raise confidence in own knowledge and skills more than they raise knowledge and skills (M/O). The intended outcome is that generalists are better able to look after PEoLC patients by themselves (O). This may, however, be accompanied, and potentially counterbalanced, by an unintended outcome that generalists refer to specialist care less than would be beneficial for patients (O). |

| Fellowes et al. 2003 | (A, M, O) Brief PEoLC training events for generalists may have unintended outcomes on specialist referrals |

This review, potential explanation for pattern of data; requires further evidence

Fellowes et al. 2003 discuss the issue that almost 70% of respondents felt they had sufficient expertise to provide palliative care while only 13% had a recognised qualification in it (see immediately above). The authors, however, do not link this configuration to a further finding on training, namely that 91.8% of respondents had attended palliative or terminal care study days.

Could it be that brief training initiatives raise confidence more than they improve knowledge and skills, resulting in decisions not to refer when this would have been the best course of action? If this is, indeed, an unintended consequence observed in some cases, is its occurrence...
### 2.4. Family and informal carer needs as a primary reason for referring to specialist services and for the timing of the referral

The needs of the family and informal carers may be the primary trigger for referring to specialist PEoLC community services (M). While this is an appropriate referral trigger (A), the referral might nonetheless be considered delayed (O) by specialists if the needs of the dying patient, e.g. of symptom control, are assessed by them as having required earlier expert involvement (M).

At the same time, some families may have declined earlier offers of involvement of specialist PEoLC community services (M/C), constraining the referral choices of generalist staff (O).

<table>
<thead>
<tr>
<th>Factors impacting on family or carers</th>
<th>% (number of respondents)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety/ other psychological problems</td>
<td>64.8% (810)</td>
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<tr>
<td>Practical problems</td>
<td>62.8% (814)</td>
</tr>
<tr>
<td>Social problems</td>
<td>59.9% (819)</td>
</tr>
<tr>
<td>Other physical problems</td>
<td>57.1% (798)</td>
</tr>
<tr>
<td>Pain</td>
<td>42.6% (829)</td>
</tr>
<tr>
<td>Communication problems</td>
<td>34.0% (801)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Factors that influence “often” the timing of referral</th>
<th>% (number of respondents)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Needs of family/carer</td>
<td>96.5% (868)</td>
</tr>
<tr>
<td>Stage of disease</td>
<td>86.8% (838)</td>
</tr>
<tr>
<td>Timing of referral of patient to me</td>
<td>34.3% (796)</td>
</tr>
<tr>
<td>Workload of local Marie Curie nurses</td>
<td>10.6% (802)</td>
</tr>
</tbody>
</table>

**Fellowes et al. 2003**

**Family and carer needs as the primary trigger for referrals to specialist PEoLC community services**

**Setting/ participants** UK, Marie Curie Nursing Service  
**Methods, brief** Questionnaire completed by 879 District Nurses (64%).  
**See 2.2. for details**

### Factors impacting on family or carers

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<tr>
<th>Reason</th>
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### Factors that influence “often” the timing of referral

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</tr>
<tr>
<td>Workload of local Marie Curie nurses</td>
<td>10.6% (802)</td>
</tr>
</tbody>
</table>
### 2.5. Terminal stage as the other primary reason for referring to specialist services

While PEOLC community services may be targeted at patients with a broad range of needs—e.g. pain relief and symptom control while curative treatments are still ongoing, all palliative care stages, the whole last year of life, etc. (A/C), generalists may consider such services seriously only in the last few months, weeks or even days of life (M/C), potentially prompted by the growing needs for support of families and carers (M/C, see 2.4). As a result, referrals occur most often in terminal stages (O).

<table>
<thead>
<tr>
<th>My workload</th>
<th>3.3% (819)</th>
</tr>
</thead>
</table>

#### (C) Trajectory of family preferences of patient referral

Fellowes et al. 2003

“[A] referral at a late stage was often at the wishes of the family who did not want MCNS input earlier.”

“[A] significant number of district nurses stated that the patient’s and his or her family’s unwillingness to have the service was a reason for non-referral.”

#### (O) Referrals as occurring most often in terminal stages

Fellowes et al. 2003 (details in 2.2; raw numbers below are for number of valid responses to a particular question)

**Timing of referral relative to disease stage/proximity to death (responses ‘often’)**

- Soon after diagnosis of incurable illness: 8.6% (799)
- When palliative care needed: 47.7% (819)
- When terminal care needed: 88.3% (849)
- When end-stage care needed: 94.6% (857)

#### (C) Service specifications are for a far broader range of needs and a lengthier timeline

Fellowes et al. 2003

---

“MCNS state that the service is available for any patient with a palliative care need (Box 1), yet less than half of district nurses (47.7 per cent) said they would often consider referring patients during the palliative phase.”

**Interaction between terminal stage and family needs in decisions for referral**

Fellowes et al., 2003

Authors’ explanation for pattern of data

“The impression given is that consideration for referral is focused on the terminal and end stages of illness. This in itself is not surprising as these are the times when patient dependency and the support needs of the carers are at their highest.”

<table>
<thead>
<tr>
<th>2.6.</th>
<th>Impact of the increasing availability of curative therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>C, M, O</td>
<td>The increasing availability of curative therapies (C), and of oral preparations in particular (C), contributes to later and later referrals (O), as there is almost always a further line of therapy that can be tried (M). At the same time, only a small proportion of patients respond to such therapies (O), the gains are minimal (O), and many patients die without receiving any, or adequate, palliative care (O).</td>
</tr>
<tr>
<td>Mintzner and Zagrabbe 2007</td>
<td><strong>Increased availability of curative therapies leads to curative attempts closer and closer to the end of life. Palliative care is, as a result, delayed while the effectiveness of therapies given as second-line or beyond is limited</strong></td>
</tr>
<tr>
<td>National Cancer Institute 2020</td>
<td>(Setting/participants) United States, oncology-hospice interface, Medicare</td>
</tr>
<tr>
<td>Broader US National Cancer Institute 2020</td>
<td>(Methods) Review of the literature on antineoplastic agents from the past 10 years; review of subsample in detail – pivotal trials on newer agents in non-small cell lung cancer for effectiveness as second-line</td>
</tr>
</tbody>
</table>
therapy and beyond; review of the records of 50 patients with breast, lung and colon cancer.

Authors’ explanation of pattern of observations/data

An “increasingly significant cause of delayed referral: the proliferation of antineoplastic agents that are active, but only in a few of the patients who are treated”.

The authors suggest that “treatment closer to the end of life is an inevitability that is likely to increase with the increasing number of agents available”. They see the increased availability of oral preparations as likely to further the tendency.

At the same time only a small percentage of patients respond to therapies given as second-line or beyond (while it takes 6-12 weeks to assess response) (pp. 128-129)

(M/O) Curative care attempted closer to death

Mintzer and Zagrabbe 2007

Evidence from the review of records (50): “a median interval from the date of the last regimen given to date of death of 30 days, with a range of 3 days to 8 months” (p. 128)

(C) Increased availability of curative therapies

Mintzer and Zagrabbe 2007
| 2.6.1. | A, C, M, O | **Non-palliative professionals as responding to patient wishes for further curative attempts, in the context of ever-present uncertainty and need for hope, rather than their clinical judgement** |

Non-palliative health professionals may be judged as being overly aggressive in treatments at the end of life (M/C); resistant to palliative care (M/C); overly committed to a curative ethos (M/C); driven by a mindset of having to do something (M/C), even by a hubris that much more is within their power at the life and death line than it actually is (M/C), and Mintzer and Zagrabbe 2007 * 
Bluhm et al. 2016 **  |

|  |  | **(C, M, O) Attempts at curative treatment are frequently made following the desires of patients and families rather than an oncologist’s best judgement, yet are still meaningful in the context of ever-present uncertainty and maintaining hope in those who need it** |

Mintzer and Zagrabbe 2007  
Anecdotal evidence from personal experience that it is often patients and families that desire to try out other treatments, even when these are not recommended by the oncologist. |

Circa 2007 (year of publication), Mintzer and Zagrabbe identify 26 agents which were approved by the FDA in the preceding decade and have come to be used routinely for the treatment of a variety of malignancies.

National Cancer Institute 2020

As of Feb 2020, the A to Z list of cancer drugs of the National Cancer Institute (US) lists 561 approved drugs approved for cancer or conditions related to cancer ([https://www.cancer.gov/about-cancer/treatment/drugs](https://www.cancer.gov/about-cancer/treatment/drugs)). Update, Aug 2021: the number has increased to 641.

**O** Limited effectiveness of therapies given as second-line or beyond

Note, the review team: This category of relevant evidence was prompted by actual evidence in Mintzer and Zagrabbe 2007. However, as it came from only 3 trials and the paper is now approaching 15 years since data collection, we chose to indicate it as a necessary type of evidence but not include the data.
| patients are subjected to unnecessary interventions (A/O), which prolong suffering rather than life (O).
| While this may be a valid line of explanation in some cases, it interacts in complex ways with a far less judgemental one:
| A key driver of decisions to continue with curative treatments (A) are often the wishes of the patient and their family (M) rather than a non-palliative professional’s clinical judgement (M). At the same time, following the former is a meaningful choice in a context of increasing treatment options (C), an awareness that there is always the off-change, the 1% uncertainty, the miracle even (C), and the value of hope till the very end for some patients and families (C). Persevering with a curative course of action very close to the end of life may be further supported by a non-palliative professional’s own difficult emotions (M/C). These are often easier to manage by “doing something” and responding to the patient wishes and preferences for trying once more than by accepting that the patient is dying (M).
| Bluhm et al. 2016
(Setting/ participants) US Midwest; oncologists from three types of settings: academic, private practice, and an oncology fellowship program. All participants routinely prescribed cytotoxic chemotherapy.
(Methods) Recruitment through physicians and administrators known to study team. Semi-structured face-to-face interviews with 17 oncologists. Qualitative content analysis. Reading and rereading of 3 transcripts by 2 team members, coding scheme developed on the basis of them. Line-by-line coding of the same transcripts by both team members; discussion; independent coding of transcripts 4-6; final coding scheme agreed, analysis completed by one team member.

| “Usually I think if physicians end up treating to the death bed, which we sometimes do, it’s because the family or the patient [is] very insistent.”

| “And so when the patient and their family [are] saying ‘Well, is there anything else,’ you sort of feel like who are you to close that door, [be]cause you actually don’t know with 100% certainty.”

| “He’s in the ICU, he’s actively dying, and he’s telling us, ‘Please don’t stop the chemotherapy.’ You know what I mean? So his fight, that’s what made him happy. I think if we hadn’t treated him, we’d have felt better, but we might have kind of killed him in a way then, too.”

| “I know a colleague who treats to the grave, and I think he tries to have these conversations with patients about end of life, but he always wants to present some hope, [be]cause you do. You want to balance reality with hope, and I think in his case, it always comes out
in such a way that people choose the hope side and go home with a prescription.”

[M/C] Perceptions of oncologists as overly aggressive in their attempts for curative treatment even when palliation would have been the far better option

Mintzer and Zagrabbe 2007

(in the context of discussing the proliferation of new therapies and the above anecdotal evidence) “Some have perceived oncologists as being overly aggressive with treatment. Often the use of chemotherapy or newer targeted therapies that, in retrospect, have been given close to the end of life is viewed as an error in judgment.” (128)

[M/C] Curative and “do something” ethos amongst oncologists

Bluhm et al. 2016

“I didn’t go into medicine to help people die.”

“That’s not just hard for them [patients] to handle, that’s hard for us to handle. We see that every day. We don’t want to tell somebody we can’t do anything for them. So it’s not just what they expect but also what we expect and maybe not being able to deal with the shortcomings of our practice ... the bottom line is, you feel bad when you don’t have anything to offer someone.”

“Sometimes there is this urge like you have to offer something [be]cause you’re called to be the oncologist.”
“That’s how we think. That’s how oncologists are trained to think. They have to offer people something.”

(M/C) Oncologists’ challenge of managing their own difficult emotions

Bluhm et al. 2016

“Clinical factors take priority in determining late chemotherapy decisions when clear treatment choices exist. When clinical factors are ambiguous, emotion becomes a highly salient influence. Oncologists view late chemotherapy to be patient driven and use it to palliate emotional distress and maintain patient hope even when physical benefit is unexpected. Oncologists experience unique and difficult challenges when caring for dying patients, including emotionally draining communication, overwhelming responsibility for life/death, limitations of oncology to heal, and prognostic uncertainty. These challenges are also eased by offering late chemotherapy.”

“Before I walk in the door and I know I’m going to do this, I still take a deep breath and walk in. And when I leave I still say my own little things in my head to myself, even when the shtick gets rote…. Believe me, there are times where I feel like I’m having an out-of-body experience because the things I’m saying are coming out so routinely that I almost feel like I’m listening to myself or watching myself. And seeing people’s reactions when you do that is emotionally draining no matter how many times you’ve done it, okay? It still is.”

“I see those [test results] and my stomach just turns, you know. It’s just so wrenching.”

“It’s pretty emotional, it’s pretty intense in the room. You can kind of feel the heaviness, and it almost feels like every time you do this, a ton of bricks has fallen on top of you, if you let yourself go there.”
(M/C) The burden of what some oncologists perceive as ultimately their decision and responsibility of deciding when to “let” a patient die

Bluhm et al. 2016

“What depresses me is not that patients die. I know that. It is how I have to actively make the decision about when I’m going to let that happen. That’s what gets so hard, year after year, after year, is being, in a way, like God. It’s like looking at somebody you’re taking care of for awhile, a long time sometimes, and thinking to yourself, you know what, it’s just time for this guy to die. And that’s a hard decision [be]cause basically it’s my decision.”

(M/C) The background awareness that there is uncertainty; that the off-chance, 1%, “miracle” at the end of life has happened before and could happen again

Bluhm et al. 2016

“[I]f the crystal ball is telling me this guy is going to die in a week no matter what you do, you don’t treat him. Period. But it’s just not always that clear cut.”

“I wish I had been able to say, “Let’s not pursue chemotherapy,” but at the same time, it was just that, what if? What if, what if, what if?”

“Sometimes while people are at death’s door they get better. Maybe 1% are going to be cured and 99% will be dead in a month, but you don’t have a way of knowing that. Would you withhold it if the patient wanted it?”
"You hear the attending physicians talk about that one person who really wanted treatment and they thought, there’s no way they’re ever gonna benefit from this. And sure enough, their disease responds and they have control, and the lung cancer patient that you thought was gonna be dead in 2 months is now alive at 2 years. I mean they’re not many here. You can count [th]em on one hand. But there’s always that story.”

<table>
<thead>
<tr>
<th>2.6.2.</th>
<th>Discipline-specific levels of awareness of treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td>C, M, O</td>
<td>Palliative care specialists (C) will be, typically, less aware (M) of innovative curative therapies in comparison to colleagues in the respective branches of medicine with curative goals (C). This too may result in conflict and antagonism about appropriate practices and timelines for PEOlC referrals (O/M/C).</td>
</tr>
<tr>
<td>Mintzer and Zagrabbe 2007</td>
<td>(M, C, O) Different levels of awareness of new curative options associated with a health professional’s specialty, also leading to interprofessional tensions</td>
</tr>
<tr>
<td>Mintzer and Zagrabbe, 2007</td>
<td>“Although those working in palliative care may be somewhat aware of these advances, palliative care professionals may not be aware of how many new agents have recently become available nor of the implications of these newer therapies in delaying hospice referrals.” “Failure to recognize this phenomenon will also result in increased frustration and sometimes antagonism between oncologists and palliative care/hospice providers.”</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2.7.</th>
<th>System-level factors affecting late referral or non-referral</th>
</tr>
</thead>
<tbody>
<tr>
<td>C, M, O</td>
<td>Referral decisions (O intermediate) may be affected by a range of factors associated with the structure and functioning of the health service and its entities (M/C):</td>
</tr>
<tr>
<td>Fellowes et al. 2003</td>
<td>(C, M) Contribution of ‘other’ factors to referral decisions and their timing</td>
</tr>
<tr>
<td>Fellowes et al. 2003 (also in 2.2 and 2.4.)</td>
<td>(M/C) Timing of preceding referral</td>
</tr>
<tr>
<td>(Setting/participants) UK, Marie Curie Nursing Service</td>
<td></td>
</tr>
<tr>
<td>(Methods) Study-specific questionnaire to District Nurses in 37 community trusts (4 randomly selected, stratified for urban/rural, per each of the 10 Marie Curie Nursing Service districts in the UK). Questionnaires sent randomly to 40 or all (if less) DNs within a participating trust. 879 out of 1,379 surveys (64% response rate). A significant number of missing responses to some questions, but also almost 250 DNs provided additional, free-text comments.</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td></td>
</tr>
<tr>
<td>34.3% of responding DNs state the time a patient has been referred to them influences their timing of referral.</td>
<td></td>
</tr>
<tr>
<td>11.8% state that referrals are often delayed or prevented as a patient has been referred too late to them to refer onwards.</td>
<td></td>
</tr>
<tr>
<td>(M/C) Experiences of own and perceptions of others’ workload</td>
<td></td>
</tr>
<tr>
<td>Fellowes et al. 2003</td>
<td></td>
</tr>
<tr>
<td>10.6% state that workload of local Marie Curie nurses influences their timing of referral, while 3.3% state this of their own workload.</td>
<td></td>
</tr>
<tr>
<td>(M/C) Lack of confidence in PEoLC services</td>
<td></td>
</tr>
<tr>
<td>Fellowes et al. 2003</td>
<td></td>
</tr>
<tr>
<td>7.6% of respondents “indicated that late referral or non-referral of patients was due to the belief that the local MCNS could not provide appropriate care”</td>
<td></td>
</tr>
<tr>
<td>(explanation for pattern of data) “The relatively small proportion of nurses who indicated they would refer patients with pain and communication problems seems to indicate a lack of confidence in the skills and knowledge of the MCNS.”</td>
<td></td>
</tr>
</tbody>
</table>

patterns (O\textsubscript{intermediate}) across individuals and teams (C).

Importantly, overall high positive perceptions of a service (C) do not ‘switch off’ factors which delay or limit (M) referrals (O\textsubscript{intermediate}).

“There may also be a lack of awareness that all grades of MCNS staff are expected to complete a recognised qualification in palliative care on appointment and to attend regular updates.”

**(M/C) Concerns about overspending**

Fellowes et al. 2003

7.0% of respondents express concern that they would overspend on Marie Curie nurses.

“A minority of district nurses had only limited use of the MCNS, stating that ... [they] were restricted in the frequency of referral for financial reasons.”

**(M) Challenges of using referral system and processes**

Fellowes et al. 2003

9.5% of respondents reported frequent delays or obstruction of referrals due to booking system.

“Some district nurses attributed unavailability to both a shortage of nurses and to NurseLink, which they perceived as distant and inflexible in dealing with local needs.”

“A small number of respondents commented on other aspects of communication, such as ... the extent of details required at referral.”

**(M/C) Referral to other services**

Fellowes et al., 2003
<table>
<thead>
<tr>
<th>22.3 % of respondents reported referring to a Macmillan nurse.</th>
</tr>
</thead>
<tbody>
<tr>
<td>“When asked for any other reasons that had prevented or delayed referral to the MCNS, the main reason given was referral to other professionals such as local services.”</td>
</tr>
</tbody>
</table>

(M/C) Accounting for and dissatisfaction with service limitations

Fellowes et al., 2003

46.0% reported that referrals are often delayed or prevented because the service has no capacity (no Marie Curie nurse available) when needed.

“However, district nurses expressed some dissatisfaction over the availability of the MCNS for rural areas, for holiday periods, for day care, for regular respite care, and for care at short notice.”

(M/C) The need to coordinate care provision from several services

Fellowes et al. 2003

“They also highlighted problems that arose when trying to coordinate a number of palliative care services for 24-hour care.”

“Unfortunately, Marie Curie cannot provide 24-hour care in exceptional circumstances. With help from Social Work Department and Hospice at Home, a complete package of care can be provided ... it’s very stressful for district nurses not knowing until the last minute what care can be provided, but overall the service is wonderful.” (free-text response)
### 2.8. IT systems and their potential for improving referrals at the end of life

- **Note, the review team**: PEoLC interventions whose programme theories involve the use of information technology are highly prominent in the UK, with a national drive to develop Electronic Palliative Care Coordination Systems since 2008. In another study of members of this team, we have identified over 500 challenges to and over 320 drivers of developing and implementing EPaCCS and data sharing projects more broadly. The articulation of CMOs around IT systems in PEoLC is a significant independent project.

### 2.9. Early referral for home care in relation to home death

**Early referral for home care (A)** may reduce the likelihood that a patient dies at home (O). This may be because families and/or professionals find it difficult to sustain care at home for extended periods of time (M).

- **Higginson and Wilkinson 2002**

  Early referral – lesser likelihood of home death

  (Setting/participants) Marie Curie Nursing Services in the UK (all four countries). At the time (late 90s) 5000 part-time nurses providing hands-on 24-hour palliative nursing care (though not specialist) for patients with advanced and progressive cancer and their families, particularly in period leading up to death; registered, enrolled nurses or care assistants; referral through primary care team, particularly district nurses.

  **NB:** 2019 numbers of Marie Curie nurses are roughly half that figure, although hours unclear – 2,160


  (Methods) Data from the Marie Curie NurseLink system used by 147 out of 220 NHS trusts using Marie Curie nurses (67%; 65% of Marie Curie Nursing Services budget); data collected on all patients referred to the service between 1 Jan 1997 and 28 Feb 1999

  26 months total of 26,632 patients;

Data on cancer death registrations in England for 1997, from ONS (Office of National Statistics); statistical analysis – frequency distributions, univariate analysis and multivariate analysis on predictors of not dying at home;

High level of missing data for place of death (recorded 13,311, missing for 13,321) and of these 94% died at home.

Shorter time between referral and death found to be associated with home death (OR 0.99; CI 0.99–0.99, narrow CI explained by high numbers in sample).

Grande et al. 2003

(Settings/ participants) Cambridgeshire, UK; cancer patients. All National Health Service home care received in the last year of life for patients who died at home vs. patients who died in inpatient care (the latter including hospital, hospice, nursing or residential home, or in transition).

(Methods) Post hoc exploratory case-control study of 127 home deaths and 200 inpatient deaths. 16-month period. One sample of patients referred to a local Hospital at Home service for palliative care (121). The other sample of patients from a local cancer registry (206). Retrospective electronic record linkage of patients’ community and inpatient care during the last year of life (robust process of identifying and matching records).

<table>
<thead>
<tr>
<th>Service type</th>
<th>Start of service as median days before death for patients to this service in last year of life</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home death (N)</td>
<td>Inpatient death (N)</td>
<td>p=0.001</td>
</tr>
<tr>
<td>District nursing</td>
<td>71 days (104)</td>
<td>141.5 days (132)</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Service</th>
<th>Median Days (N)</th>
<th>Median Days (N)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Night nursing</td>
<td>7.5 days (32)</td>
<td>26 days (17)</td>
<td>0.001</td>
</tr>
<tr>
<td>Macmillan</td>
<td>91.5 days (40)</td>
<td>81.5 days (32)</td>
<td>non-sign</td>
</tr>
<tr>
<td>Marie Curie</td>
<td>12 days (63)</td>
<td>30.5 days (30)</td>
<td>0.008</td>
</tr>
<tr>
<td>Other community trust care</td>
<td>38 days (19)</td>
<td>58 days (18)</td>
<td>non-sign</td>
</tr>
<tr>
<td>Flexible care</td>
<td>20 days (18)</td>
<td>50.5 days (12)</td>
<td>non-sign</td>
</tr>
<tr>
<td>Hospital@Home nursing</td>
<td>6 days (51)</td>
<td>21 days (10)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

For inpatient services, data on inpatient hospice care show, in contrast, that starting care earlier is associated with home death (median of 35 days for the patients who died at home and 12 days for the patients who died as inpatients). Receiving care from the specialist hospital teams also shows a tendency towards increasing likelihood of home death (p=0.07).

**Explanation of pattern of data**

“Patients who began their home nursing early were less likely to die at home than those who began such care late. This suggests that it may be difficult to sustain end-of-life care at home for an extended period.”

“This may be due to the strain this places on informal care resources, as family carers shoulder the greater part of the burden.”

### 2.10. Earlier and later referral relative to time of diagnosis

For inpatient services, data on inpatient hospice care show, in contrast, that starting care earlier is associated with home death (median of 35 days for the patients who died at home and 12 days for the patients who died as inpatients). Receiving care from the specialist hospital teams also shows a tendency towards increasing likelihood of home death (p=0.07).

**Explanation of pattern of data**

“Patients who began their home nursing early were less likely to die at home than those who began such care late. This suggests that it may be difficult to sustain end-of-life care at home for an extended period.”

“This may be due to the strain this places on informal care resources, as family carers shoulder the greater part of the burden.”

---

patient dies at home (O). This may be because they have developed greater acceptance of their terminal prognosis (M/C) and/or because have been “through more trials, tribulations, and treatment failures, and spent more time in institutions” (M/C). They may thus be more likely to seek, accept and plan for home-based palliative care as opposed to more invasive, hospital-based care with curative or life-prolonging goals (M).

(Setting/ participants) Combined community and hospital-based palliative care service in Toronto, Ontario, Canada. Patients residing in five districts of metropolitan Toronto, within 20 km radius of base hospital. Referrals made by oncologists, surgeons and general practitioners. Patients seen initially within 24 hours of referral. Around the clock on-call coverage by the palliative care physicians (unclear if only at home). All patients receive regularly scheduled RN visits. Patients aware of terminal diagnosis and expressed a preference to die at home.

(Methods) Retrospective chart review (both medical and nursing charts) of 402 sequential cancer patients referred to service. Period between 1 Apr 1997 and 8 Apr 1999 (24 months). Further information collected at visits (e.g. number of caregivers) or from web-based sources (Toronto Real Estate Board’s web-service for home valuation). Analysis in SAS, both parametric and non-parametric.

Mean number of months between diagnosis and referral: 27.3 months, SD 2.34 for those who died at home vs. 11.6, SD 2.61 for those who died at hospital; p < 0.001. (Note it is not months before death, but between diagnosis and referral, i.e. potential “delay” in referral)

(M/C) Period of time since diagnosis in relation to acceptance of death and desire to avoid the downsides of treatment

Maida 2002

(explanation of pattern of data) Longer period of time between diagnosis and referral to palliative care physician means that such patients will have lived “with the knowledge and ramifications of their condition for longer”. This has given them the opportunity to develop greater acceptance of their terminal prognosis. Such patients have, overall, also gone “through more trials, tribulations, and treatment failures, and spent more time in institutions”. Perhaps they had a greater desire to return home finally to die. (p. 285)
3. Supplementary Table 2: Abstract-level scoping of systematic reviews on prognosis from the last 5 years (2015-2020)

This table includes core information from a scoping search on recent research on prognosis, relative to expectations that advancements in research can point towards better prognostic tools/ approaches for identifying patients at the end of life.

The search strategy is described in the Literature searching appendix (Appendix 4). We have included abstracts of papers published between 2015 and 2020. We excluded: non-systematic reviews (e.g. narrative reviews or supposedly systematic reviews using a single database); research on children; papers on procedures with curative intent and/or exclusive focus on longer survival timeframes (e.g. 5 or 10 years). In cases where overall survival at 5 or 10 years was rather low, e.g. below 20%, we did, however, include the papers. We excluded studies we have already reported on in the CMO table above.

For the needs of this preliminary scoping search, we only accessed the abstracts of papers. If the paper had no abstract or it did not provide sufficient information about its findings, it was not added to the table.

Some frequent abbreviations in the authors’ abstracts are:

OS – overall survival
DFF – disease free survival
PFS – progression free survival
RFS – relapse free survival
DSS – disease specific survival
<table>
<thead>
<tr>
<th>Reference (authors and year)</th>
<th>Condition, condition + therapy, or setting</th>
<th>No studies reviewed</th>
<th>No participants</th>
<th>Predictors of survival or predictive approach explored</th>
<th>Findings</th>
<th>Broad conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Bu et al. 2015</td>
<td>malignant tumors</td>
<td>30</td>
<td>4497</td>
<td>MicroRNA-126</td>
<td>“[H]igh level of miR-126 was a predictor for favorable survival of carcinomas, with pooled HR of 0.77 (95% CI 0.64-0.93) for OS, 0.64 (95%CI 0.48-0.85) for DFS, and 0.70 (95% CI 0.50-0.98) for PFS/RFS/DSS.” “However, high level of circulating miR-126 predicted a significantly worse OS in patients with cancer (HR = 1.65, 95% CI 1.09-2.51).”</td>
<td>Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed, but opposing valence depending on context</td>
</tr>
<tr>
<td>2. Li et al. 2015</td>
<td>non-small cell lung cancer</td>
<td>10</td>
<td></td>
<td>rapamycin (mTOR) and phosphorylated mTOR (p-mTOR)</td>
<td>“The results indicated that no statistically significant association was found between mTOR/p-mTOR expression and NSCLC patients’ prognosis.”</td>
<td>No/ insufficient/ weak evidence</td>
</tr>
<tr>
<td>3. Petrelli et al. 2015</td>
<td>survival with bevacizumab-based therapy in colorectal cancer patients</td>
<td>29</td>
<td>11,585</td>
<td>Potential prognostic factors in 3 or more source papers (see column to the right)</td>
<td>Five parameters were associated with survival in &gt;=3 papers: (1) a longer progression-free interval [PFS: HR 0.87, 95 % confidence interval (CI) 0.78-0.97; P = 0.01]; (2) a single site of metastases (HR 0.63, 95 % CI 0.56-0.71; P &lt; 0.00001);</td>
<td>Prognostic/predictive value of small set of parameters confirmed, highly specific context of condition and/or therapy</td>
</tr>
</tbody>
</table>
4. Qi et al. 2015

| Budd-Chiari syndrome | 79 studies | 1-, 5- and 10-year survival relative to treatment modality | Median 1-year survival rate: 93% after interventional radiological treatment, 81% after surgery other than liver transplantation, 82.5% after liver transplantation, 68.1% after medical therapy alone. “Bilirubin, creatinine and ascites were more frequently identified as significant prognostic factors in univariate analyses. But their statistical significance was less frequently achieved in multivariate analyses.” |

5. Tang et al. 2015

<p>| Breast cancer | 41 articles | MicroRNAs (miRNAs) – 27 types, as identified in the source studies, with “For the studies evaluating miR-21’s association with clinical outcomes, the median HR in the studies was 2.32 (interquartile range [IQR] = 1.04-3.40), and the pooled HR suggested that high expression of miR-21 has a negative Single marker (i.e. relative importance unclear), prognostic/|</p>
<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Condition</th>
<th>Sample Size</th>
<th>Factors Assessed</th>
<th>Findings</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Thuy et al. 2015</td>
<td>Glioblastoma multiforme (GBM)</td>
<td>14,678</td>
<td>39 unique genetic or molecular factors</td>
<td>Higher expression levels of miR-21 significantly predicted poorer outcome, with median HR in the reported studies of 4.07 (IQR = 1.54-4.43) and a pooled HR of 2.94 (95% CI, 2.08-4.17; p&lt;0.05).</td>
<td>Multiple (&gt;30) prognostic/predictive factors, findings unclear from abstract</td>
</tr>
<tr>
<td>7. Wang et al. 2015</td>
<td>Cancer</td>
<td>2,597</td>
<td></td>
<td>Overexpression of miR-34a may predict good overall survival ([OS], HR =0.76, 95% confidence interval: 0.55-1.06, P=0.105), but the effect was not significant enough. Subgroup analysis results showed miR-34a was an ideal predictor for digestive system cancer (OS, HR =0.50, 95% confidence interval: 0.25-0.99, P=0.048). The predictive effects of elevated expression of miR-34a on the OS of untreated and treated patients were not of obvious differences.</td>
<td>Single marker (i.e. relative importance unclear), weak evidence for overall predictive/prognostic value, strong evidence for a specific context</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Reference</th>
<th>Study Description</th>
<th>ESR</th>
<th>Prognostic Value</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.</td>
<td>Wei and Niu 2015</td>
<td>Various cancers</td>
<td>9</td>
<td>932</td>
<td>Elevated MALAT1 expression was significantly correlated with poor OS (HR 2.02; 95% CI: 1.62-2.52; P &lt; 0.001; I(2) = 0%). Subgroup analysis indicated that tumor type, histology type, ethnicity, and measurement technique did not affect the prognostic value of MALAT1 for OS. The HR of elevated MALAT1 for DFS was 2.78 (95% CI: 1.87-4.15; P &lt; 0.001; I(2) = 0%).</td>
</tr>
<tr>
<td>9.</td>
<td>Zhou C et al. 2015</td>
<td>Patients with liver diseases who have undergone transjugular intrahepatic portosystemic shunt (TIPS)</td>
<td>11</td>
<td>Comparison of the Child-Turcotte-Pugh (CTP) score and the model for end-stage liver disease (MELD) score for predicting survival in such patients</td>
<td>“In the meta-analyses, MELD score was superior to CTP score in predicting 3-month survival after TIPS (mean ES, 0.63; 95% confidence interval [CI], 0.13-1.14; P=0.01), but the predictive capability in 1-month, 6-month, and 12-month survival was not significant (1-month: mean ES, 0.79; 95% CI, -0.24-1.83; P=0.13; 6-month: mean ES, 0.46; 95% CI, -2.46-3.37; P=0.76; 12-month: mean ES, 0.36; 95% CI, -0.25-0.96; P=0.25). CONCLUSIONS: No enough evidence are confirmed so far that MELD score is better than CTP score to assess the overall prognosis after TIPS, especially long-term predictions, but 3-month predictive capability of MELD score significantly outperform CTP score.”</td>
</tr>
<tr>
<td>10.</td>
<td>Cheon et al. 2016</td>
<td>Advanced cancer</td>
<td>15</td>
<td>Clinicians’ predictions of survival</td>
<td>“Clinicians in five studies underestimated patients’ survival (estimated to observed survival ratio between 0.5 and 0.92). In contrast, 12 studies reported clinicians’ overestimation of survival (ratio between 1.06 and 6).” “CPS in advanced cancer patients is often inaccurate and overestimated.”</td>
</tr>
</tbody>
</table>

| 11. Lee et al. 2016 | early-stage endometrial cancer | 11 | positive peritoneal cytology | “In patients with surgical stage 1 or 2 early-stage endometrial cancer, the incidence of Grade 3 was higher and 5-year overall survival was worse in patients with positive peritoneal cytology compared with negative peritoneal cytology. However, the incidence of Grade 1 was lower in those with positive peritoneal cytology compared with negative peritoneal cytology. In patients with surgical stage 1 early-stage endometrial cancer, the incidence of myometrial invasion >=1/2 tended to be higher and 5-year progression-free survival was worse in the positive peritoneal cytology group than the negative peritoneal cytology group. However, the incidence of myometrial invasion <1/2 was lower in the positive peritoneal cytology group than the negative peritoneal cytology group.” | Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed, but opposing valence depending on context |
| 12. Leuzzi et al. 2016 | non-small-cell lung cancer (NSCLC) | 10 | baseline C-reactive protein (CPR) | “In overall analysis, elevated pretreatment CRP values were significantly associated with poor overall survival (HR 1.60, 95% CI 1.30-1.97, p<0.001, I² = 71.9%). Similar results were observed across considered strata. However, higher mortality risk was reported in studies in which CRP was combined with other factors (HR 1.96, 95% CI 1.58-2.45) and in those using a cutoff value of 3 mg/L (HR 1.89, 95% CI 1.52-2.35).

CONCLUSIONS: Based on our analysis, baseline high CRP level is significantly associated with poor prognosis in early-stage NSCLC. Further prospective controlled studies are needed to confirm these data.” | Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed, further research recommended |
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Description</th>
<th>Sample Size</th>
<th>Method</th>
<th>Result</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>13. Marques et al. 2016</td>
<td>Head and neck cancer</td>
<td>12</td>
<td>mTOR pathway protein immunoexpression</td>
<td>The meta-analysis revealed that the frequency of overall expression of mTOR pathway proteins was 74.42% (CI: 63.3 to 84.0, P &lt; 0.001, n = 2016 samples). The survival meta-analysis showed a pooled hazard ratio for OS and DFS of 1.44 (95% confidence interval [95% CI] 1.14-1.73) and 1.18 (95% CI 0.71-1.64), respectively.</td>
<td>Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed</td>
</tr>
<tr>
<td>14. Qian et al. 2016</td>
<td>Systemic lupus erythematosus (SLE)-associated pulmonary arterial hypertension (PAH)</td>
<td>6</td>
<td>Main study goal to assess survival of such patients; predictors as identified in literature</td>
<td>WHO Functional class (Fc) III/IV was found to be an independent prognostic factor of mortality. Higher mean pulmonary arterial pressure (mPAP), higher pulmonary vascular resistance (PVR), lower six minutes walking distance (6MWD), higher brain natriuretic peptide (BNP) and higher N-terminal proBNP (NT-proBNP) level were also related to poor survival.</td>
<td>Prognostic/predictive value of small set of parameters confirmed, highly specific context of condition and/or therapy</td>
</tr>
<tr>
<td>15. Shan et al. 2016</td>
<td>Cancer</td>
<td>44</td>
<td>Dicer status</td>
<td>24 of 44 articles revealed low Dicer status as a predictor of poor prognosis. The aggregate result of overall survival (OS) indicated that low Dicer expression level resulted in poor clinical outcomes, and subgroup of IHC and RT-PCR method both revealed the same result. Overall analysis of progression-free survival (PFS) showed the same result as OS, and both the two subgroups divided by laboratory method revealed positive results. Subgroup analysis by tumor types showed low dicer levels were</td>
<td>Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed, further research recommended</td>
</tr>
<tr>
<td>16. Wu et al. 2016</td>
<td>Cancer – 11 different tumor types</td>
<td>18</td>
<td>high mobility group box 1 (HMGB1) overexpression</td>
<td>&quot;HMGB1 overexpression was significantly associated with poorer OS (HR: 1.99; 95% CI, 1.71-2.31) and PFS (HR: 2.26; 95% CI, 1.65-3.10) irrespective of cancer types including gastric cancer, colorectal cancer, hepatocellular carcinoma, pancreatic cancer, nasopharyngeal carcinoma, head and neck squamous-cell carcinoma, esophageal cancer, malignant pleural mesothelioma, bladder cancer, prostate cancer, and cervical carcinoma. Subgroup analyses indicated geographical area and size of studies did not affect the prognostic effects of HMGB1 for OS. Moreover, HMGB1 overexpression had a consistent correlation with poorer OS when detected by immunohistochemistry in tissues and enzyme-linked immunosorbent assay in serum, whereas the correlation did not exist by quantitative real-time reverse-transcription polymerase chain reaction in tissues. HMGB1 overexpression is associated with poorer</td>
<td>Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed</td>
</tr>
<tr>
<td>Study</td>
<td>Cancer Type</td>
<td>Sample Size</td>
<td>Study Design</td>
<td>Findings</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
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<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>17. Chen et al. 2017</td>
<td>Cancer</td>
<td>652</td>
<td>Retrospective</td>
<td>“The results showed a significant positive association between HOTTIP levels and LNM (Odds ratio, OR = 2.30, 95% CI: 1.58-3.35, p &lt; 0.0001) in a fixed-effects model (I² = 0%, p = 0.949) and it could also predict poor OS in cancer patients (Hazard ratio HR = 2.24, 95% CI: 1.74-2.90, p &lt; 0.00001) in a fixed-effects model (I² = 0%, p = 0.925). In conclusion, this meta-analysis demonstrated that the higher expression level of HOTTIP is correlated with positive LNM and poor OS in different types of cancer and HOTTIP might serve as a novel predictor of LNM and survival in human cancer.”</td>
<td></td>
</tr>
<tr>
<td>18. Mahar et al. 2017</td>
<td>Colorectal cancer</td>
<td></td>
<td></td>
<td>Significant heterogeneity in colorectal cancer prognostication tool quality exists. Methodology is incompletely or inadequately reported. Evaluations of the internal or external validity of the prognostic model are rarely performed. Prognostication tools are important devices for patient management, but tool reliability is compromised by poor quality. Guidance for future development of prognostication tools in colorectal cancer is needed.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reference</th>
<th>Disease/Condition</th>
<th>Study Title</th>
<th>HRQoL Outcomes</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>20. Petrelli et al. 2017 JAMA Oncology</td>
<td>Colon cancer</td>
<td>Primary tumor location (Left-Sided vs Right-Sided)</td>
<td>“Left sided primary tumor location was associated with a significantly reduced risk of death (HR, 0.82; 95% CI, 0.79-0.84; P &lt; .001) and this was independent of stage, race, adjuvant chemotherapy, year of study, number of participants, and quality of included studies.”</td>
<td>Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed</td>
</tr>
<tr>
<td>21. Petrelli et al. 2017 Urology</td>
<td>radical nephroureterectomy for upper urinary tract urothelial carcinoma</td>
<td>Prognostic factors that influence overall survival described in the literature</td>
<td>“The clinicopathological factors associated with an increased risk of death were age, multifocality, lymphovascular invasion, pT3-4 stage, pT2 vs &lt;pT2 stage, node-positive disease, tumor grade, tumor size, and positive surgical margins.”</td>
<td>Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed</td>
</tr>
<tr>
<td>22. Smith et al. 2017</td>
<td>COPD</td>
<td>known prognostic variables and scores that predict prognosis in COPD, specifically including variables that contribute to risk assessment of patients for death within 12 months</td>
<td>“No multivariable indices were developed with the specific aim of predicting all-cause mortality in stable COPD within 12 months. Only nine indices were identified from four studies, which had been validated for this time period. Tools developed using expert knowledge were also identified, including the Gold Standards Framework Prognostic Indicator Guidance, the RADboud Indicators of Palliative Care Needs, the Supportive and Palliative Care Indicators Tool and the Necesidades Paliativas program tool. CONCLUSION: A number of variables contributing to the prediction of all-cause mortality in COPD were identified. However, there are very few studies that are designed to”</td>
<td>Tools (scores, indices) – unspecific</td>
</tr>
<tr>
<td>Study</td>
<td>Type of Cancer</td>
<td>Patients</td>
<td>Method</td>
<td>Description</td>
</tr>
<tr>
<td>-------</td>
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</tr>
<tr>
<td>23. Urun et al. 2017</td>
<td>advanced urothelial cancer treated with platinum based chemotherapy</td>
<td>13</td>
<td>1475</td>
<td>excision repair cross-complementing group 1 (ERCC1)</td>
</tr>
<tr>
<td>24. Yang et al. 2017</td>
<td>epithelial ovarian cancer</td>
<td>12</td>
<td>3,154</td>
<td>neutrophil-to-lymphocyte ratio (NLR)</td>
</tr>
</tbody>
</table>

**Assess, or report, the prediction of mortality at or less than 12 months. The quality of evidence remains low, such that no single variable or multivariable score can currently be recommended.**
25. Zabaleta et al. 2017  
**pulmonary metastasectomy in colorectal cancer patients**  
28  
**history of resected liver metastases**  
"In more than half of the papers analyzed (63.2%), patients with a history of resected liver metastases had a lower survival rate than those who did not have such a history, and the difference was statistically significant in eight of these studies. However, data were presented differently, and authors reported mean survival time, survival rates, or hazard ratios.

CONCLUSIONS: A history of liver metastases seems to be a negative prognostic factor, but the individual data need to undergo a meta-analysis.”

26. Zhang et al. 2017  
**Colorectal cancer**  
23  
**Metabolomic profile of patients**

"Metabolites related to cellular respiration, carbohydrate, lipid, protein and nucleotide metabolism were significantly altered in CRC. Altered metabolites were also related to prognosis, survival and recurrence of CRC. This review could represent the most comprehensive information and summary about CRC metabolism to date. It certifies that metabolomics had great potential on both discovering clinical biomarkers and elucidating previously unknown mechanisms of CRC pathogenesis.”

27. Zhao et al. 2017  
**pulmonary metastasectomy in renal cell cancer patients**  
16  
1447  
**prognostic factors as identified in the literature**

"The poor prognostic factors were lymph node involvement (LNI) of primary RCC (HR 3.44, 95% confidence interval (CI) 1.78-6.67, P = 0.001), incomplete resection of metastases (HR 3.74, 95% CI 2.49-5.61, P = 0.000), multiple metastases (HR 1.55, 95% CI 1.18-2.03, P = 0.002), larger metastases (HR 1.45, 95% CI 1.26-1.66, P = 0.000), LNI of metastases (HR 3.06, 95% CI 1.52-6.19, P = 0.002), synchronous

Prognostic/ predictive value of small set of parameters confirmed, highly specific context of condition and/or therapy
<table>
<thead>
<tr>
<th>Study Authors/Year</th>
<th>Tumor Type</th>
<th>Study Design</th>
<th>Prognostic Factors</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bollen et al. 2018</td>
<td>Spinal bone metastases</td>
<td>43 different prognostic factors investigated in included studies, of which 17 were relevant to pre-treatment survival estimation.</td>
<td>&quot;The prognostic factors most frequently associated with survival were the primary tumor and the performance status. The prognostic factors most frequently not associated with survival were age, gender, number and location of the SBM and the presence of a pathologic fracture. Conclusions: Prognostication for patients with SBM should be based on an accurate primary tumor classification, combined with a performance score. The benefit of adding other prognostic factors is doubtful.&quot;</td>
<td>Familiar parameters validated from a large number of candidates</td>
</tr>
<tr>
<td>Bosma et al. 2018</td>
<td>Ewing sarcoma</td>
<td>24 prognostic factors investigated, 14 relevant for this review</td>
<td>&quot;Prognostic factors associated with survival include metastasis at diagnosis, large tumors (volume&gt;=200ml or largest diameter&gt;=8cm), primary tumors located in the axial skeleton, especially pelvic and a histological response of less than 100%. These factors should be included as risk factors in the development of prediction models for ES.&quot;</td>
<td>Prognostic/predictive value of small set of parameters confirmed, highly specific context of condition and/or therapy</td>
</tr>
<tr>
<td>Chi et al. 2018</td>
<td>Cancer</td>
<td>Albumin to globulin ratio (AGR)</td>
<td>&quot;The analysis based on random-effect model demonstrated that low AGR was significantly associated with poor OS in various cancers (HR=1.87, 95% CI 1.50-2.34; P &lt; 0.001).&quot; &quot;[A] large scale of samples and prospective studies are needed in the future to validate the role of AGR in practice.&quot;</td>
<td>Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed, further research recommended</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Cancer Type</th>
<th>Sample Size</th>
<th>Gene</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dan et al. 2018</td>
<td>Cancer</td>
<td>11</td>
<td>miR-375</td>
<td>&quot;The pooled HR for overall/cumulative survival (OS/CS) was 1.90 (95% confidence interval (CI) 1.57-2.29) and the pooled HR for disease-free, recurrence-free or progression-free survival (DFS/RFS/PFS) was 1.93 (95% CI 1.39-2.67), indicating low miR-375 expression was associated with significantly poorer outcomes compared to normal/high miR-375 expression. Subgroup analysis revealed miR-375 might be a good prognostic factor in cancer, regardless of population, sample type, and cancer type. The prognostic value of miR-375 in non-Chinese patients was particularly high (pooled HR &gt; 2). CONCLUSION: Low miR-375 expression could represent a valuable prognostic marker in various cancers. Circulating miR-375 levels may provide a useful non-invasive, practical prognostic biomarker. However, the prognostic value of miR-375 in specific cancer types remains unclear; further studies are warranted.&quot;</td>
</tr>
<tr>
<td>Georgakis et al. 2018</td>
<td>Gliomatosis cerebri (GC)</td>
<td>523 patient level data</td>
<td></td>
<td>The median OS and PFS were 13 and 10 months, with 5-year rates of 18% and 13%, respectively. Age &gt;=65 years at diagnosis (hazard ratio for OS HR&lt;sub&gt;OS&lt;/sub&gt;, 2.32; 95% confidence interval [CI], 1.62-3.31), high-grade tumor (HR&lt;sub&gt;PFS&lt;/sub&gt; for grade III, 1.57; 95% CI, 1.02-2.40; HR&lt;sub&gt;PFS&lt;/sub&gt; for grade IV, 1.74; 95% CI, [0.98-3.10]), Prognostic/predictive value confirmed (16 factors)</td>
</tr>
</tbody>
</table>
GC type II (HR$_{OS}$, 1.49; 95% CI, 1.12-1.98; HR$_{PFS}$, 1.56; 95% CI, 1.04-2.34),

more central nervous system (CNS) regions involved (HR$_{OS}$, 1.09; 95% CI, 1.01-1.18),

focal neurological deficits (HR$_{OS}$, 1.41; 95% CI, 1.07-1.86),

cerebellar symptoms (HR$_{PFS}$, 2.20; 95% CI, 1.42-3.39),

more symptoms at presentation (HR$_{OS}$, 1.21; 95% CI, 1.05-1.40),

Karnofsky performance scale score <70 (HR$_{OS}$, 3.58; 95% CI, 1.73-7.39; HR$_{PFS}$, 4.48; 95% CI, 1.39-14.4),

magnetic resonance imaging contrast enhancement (HR$_{OS}$, 1.48; 95% CI, 1.12-1.96; HR$_{PFS}$, 1.74; 95% CI, 1.18-2.55),

symmetric bilateral CNS invasion (HR$_{OS}$, 1.42; 95% CI, 1.03-1.96),

and high proliferation index (Ki-67 >5%; HR$_{OS}$, 2.32; 95% CI, 1.11-4.86)

were independent predictors of poor outcomes.

In contrast,
<table>
<thead>
<tr>
<th>Study</th>
<th>Cancer Type</th>
<th>n</th>
<th>Sample Size</th>
<th>Result</th>
<th>Marker/Marker Type</th>
<th>Prognostic/Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang et al. 2018</td>
<td>Lung cancer</td>
<td>55</td>
<td>22,719</td>
<td>Decreased pretreatment haemoglobin level</td>
<td>The results indicated that decreased haemoglobin level was significantly associated with poor overall survival of patients with lung cancer (HR 1.51, 95% CI 1.42-1.61), both in non-small cell lung cancer (HR 1.57, 95% CI 1.44-1.72) and in small cell lung cancer (HR 1.56, 95% CI 1.21-2.02). We also found that the lower the haemoglobin level, the shorter was the overall survival of patients with lung cancer (HR 1.11, 95% CI 1.06-1.16.”</td>
<td>Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed</td>
</tr>
<tr>
<td>Kloter et al. 2018</td>
<td>Cancer</td>
<td>19</td>
<td></td>
<td>Heart rate variability</td>
<td>“[H]igher HRV correlated positively with patients’ progression of disease and outcome. Thus, we conclude that individuals with higher HRV and advanced coping mechanisms seem to have a better prognosis in cancer progression.”</td>
<td>Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed</td>
</tr>
</tbody>
</table>

**References:**

1. Huang et al. 2018
2. Kloter et al. 2018
<table>
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<tbody>
<tr>
<td>35. Lakshminarayana et al. 2018</td>
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<tr>
<td>36. Li et al. 2018</td>
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<tr>
<td>37. Liu et al. 2018</td>
</tr>
<tr>
<td>38. Montagnani et al. 2018</td>
</tr>
<tr>
<td>---------------------------</td>
</tr>
<tr>
<td>liver resection in metastatic gastric cancer (GC)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>39. Pereira et al. 2018</th>
<th>Prognostic/predictive value of small set of parameters confirmed, highly specific context of condition and/or therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced cancer (metastatic disease)</td>
<td>“Our analysis demonstrates a 5yOS rate of 22% (95%CI: 18-26%) and 10yOS rate of 11% (95%CI: 7-18%) among patients undergoing radical hepatectomy. A favorable effect on OS was shown by several factors linked to primary cancer (lower T and N stage, no lympho-vascular or serosal invasion) and burden of hepatic disease (&lt;3 metastases, unilobar involvement, greatest lesion&lt;5cm, negative resection margins). Moreover, lower CEA and CA19.9 levels and post-resection chemotherapy were associated with improved OS.”</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>38. Montagnani et al. 2018</th>
<th>Prognostic factors identified in the literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>liver resection in metastatic gastric cancer (GC)</td>
<td>“Our analysis demonstrates a 5yOS rate of 22% (95%CI: 18-26%) and 10yOS rate of 11% (95%CI: 7-18%) among patients undergoing radical hepatectomy. A favorable effect on OS was shown by several factors linked to primary cancer (lower T and N stage, no lympho-vascular or serosal invasion) and burden of hepatic disease (&lt;3 metastases, unilobar involvement, greatest lesion&lt;5cm, negative resection margins). Moreover, lower CEA and CA19.9 levels and post-resection chemotherapy were associated with improved OS.”</td>
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</table>

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<tr>
<th>39. Pereira et al. 2018</th>
<th>Prognostic/predictive value of small set of parameters confirmed, highly specific context of condition and/or therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced cancer (metastatic disease)</td>
<td>“Low PA was associated with worse nutrition status evaluated by body mass index, serum albumin level, transferrin, and fat-free mass. The median OS of the included papers varied from 25.5–330 days, and all studies analyzed showed a significant association between PA and OS, in that patients with low PA had worse OS. Future studies are necessary to justify the use of PA in therapeutic decisions for this population and to evaluate whether nutrition Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed, further research recommended”</td>
</tr>
</tbody>
</table>

### 40. Pinart et al. 2018

| metastatic castration-resistant prostate cancer | 12 | 8750 | Prognostic models identified in the literature | “Models included 4-11 predictor variables, mostly hemoglobin, baseline PSA, alkaline phosphatase, performance status, and lactate dehydrogenase. Very few incorporated Gleason score. Two models included predictors related to docetaxel and mitoxantrone treatments. Model performance after internal validation showed similar discrimination power ranging from 0.62 to 0.73. Overall survival models were mainly constructed as nomograms or risk groups/score. Two models obtained an overall judgment of low risk of bias. CONCLUSIONS: Most models were not suitable for clinical use due to methodological shortcomings and lack of external validation. Further external validation and/or model updating is required to increase prognostic accuracy and clinical applicability prior to their incorporation in clinical practice as a useful tool in patient management.” | Most models not suitable for clinical use; further validation/updating required |

### 41. ter Veer et al. 2018

| metastatic oesophagogastric cancer | 46 | 15,392 | Prognostic and predictive factors as | “Prognostic factors were identified from multivariate regression analyses in study reports. Factors were considered potentially | Multiple factors – potentially |

---

identified in the source studies

clinically relevant if statistically significant (P ≤ 0.05) in multivariate analysis in ≥50% of the total number of patients in the pooled sample of the RCTs and were reported with a pooled sample size of ≥600 patients in the first-line or ≥300 patients in the beyond first-line setting. Predictive factors were identified from time-to-event stratified treatment comparisons and deemed potentially clinically relevant if the P-value for interaction between subgroups was ≤0.20 and the hazard ratio in one of the subgroups was significant (P ≤ 0.05).”

“Seventeen prognostic factors for overall survival in the first-line and four in the beyond first-line treatment setting were potentially clinically relevant. Twenty-one predictive factors in first-line and nine in beyond first-line treatment setting were potentially relevant regarding treatment efficacy.”

“The prognostic and predictive factors identified in this systematic review can be used to characterise patients in clinical practice, be included in future trial designs, enrich prognostic tools and generate hypotheses to be tested in future research to promote patient-centred treatment.”

<table>
<thead>
<tr>
<th>Prognostic factors as identified from the source studies</th>
<th>Prognostic factors as identified from the source studies</th>
<th>Prognostic factors as identified from the source studies</th>
<th>Prognostic factors as identified from the source studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>42. Wang C et al. 2018 pulmonary metastasectomy in liver cancer</td>
<td>17 513 Prognostic factors as identified from the source studies</td>
<td>“The poor prognostic factors were disease-free interval (DFI) &lt; 12 months (HR = 2.421 95% CI 1.384 4.236) and existence of cirrhosis (HR = 1.936 95% CI 1.031 3.636).”</td>
<td>Familiar parameters validated from a large number of candidates</td>
</tr>
</tbody>
</table>
Prognostic factors as identified from the source studies

The following survival predictors of ECPR were identified:

- out-of-hospital cardiac arrest (CA) (OR 0.58, 95% CI 0.36-0.93, P = .02)
- in-hospital CA (OR 1.73, 95% CI 1.08-2.77, P = .02)
- witnessed CA (OR 5.2, 95% CI 1.18-22.88, P = .01)
- bystander cardiopulmonary resuscitation (CPR) (OR 7.35, 95% CI 2.32-23.25, P < .01)
- initial shockable rhythm (OR 2.29, 95% CI 1.53-3.42, P < .01)
- 1st recorded nonshockable rhythm (OR 0.44, 95% CI 0.29-0.66, P < .01)
- CPR duration (MD -13.84 minutes, 95% CI -21 to -6.69, P < .0001)
- arrest-to-extracorporeal membrane oxygenation (ECMO) (MD -17.88 minutes, 95% CI -23.59 to -12.17, P < .01)
- PH (MD 0.14, 95% CI 0.08-0.21, P < .01)
- lactate (MD -3.66 mmol/L, 95% CI -7.15 to -0.17, P = .04)
- percutaneous coronary intervention (PCI) (OR 1.63, 95% CI 1.02-2.58, P = .04).

Prognostic/predictive value confirmed (11 factors)
<table>
<thead>
<tr>
<th>Reference</th>
<th>Disease Type</th>
<th>N</th>
<th>Year</th>
<th>Gene/Marker</th>
<th>Result</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>44. Yang et al. 2018</td>
<td>Breast cancer</td>
<td>11</td>
<td>2018</td>
<td>Circulating cell-free DNA (cfDNA)</td>
<td>cfDNA was shown to be significantly associated with PFS (HR 2.02, 95% CI 1.51-2.72, ( P &lt; .001 ), I = 82%) and OS (HR 1.75, 95% CI 1.01-3.05, ( P &lt; .001 ), I = 92%). The results of subgroup analyses also revealed that cfDNA was a good predictor of prognosis in breast cancer patients. CONCLUSION: Our meta-analysis indicated that cfDNA was associated with poor PFS and OS, thus it may help to predict outcomes of patients with breast cancer. However, further studies are needed to confirm our results.</td>
<td>Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed, further research recommended</td>
</tr>
<tr>
<td>45. Zhang et al. 2018</td>
<td>Cancer</td>
<td>10</td>
<td>2018</td>
<td>LINC00152, a novel long noncoding RNA (IncRNA)</td>
<td>Elevated LINC00152 could predict unfavorable OS with pooled HR of 1.66 (95% CI: 1.29-2.13, ( p &lt; .0001 )) and poor DFS (HR=2.13, 95% CI: 1.39-3.25, ( p=.0005 )) in cancer patients. CONCLUSION: LINC00152 was correlated with advanced clinicopathological features and poor prognosis as a novel predictive biomarker in various cancers.</td>
<td>Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed, novel factor, further research required</td>
</tr>
<tr>
<td>46. Aleksova et al. 2019</td>
<td>Heart transplantation</td>
<td>21</td>
<td>2019</td>
<td>Risk prediction scores – 16 identified in the literature</td>
<td>Seven (44%) scores were validated in external cohorts and 8 (50%) assessed model performance. Overall model discrimination ranged from poor to moderate (C-statistic/area under the receiver operating characteristics 0.54-0.77). The IMPACT score was the most widely validated, was well calibrated in two large registries, and was best at discriminating 3-month survival (C-statistic 0.76). Most scores did not perform particularly well in any cohort in which they were assessed. This review shows that there are insufficient data to recommend</td>
<td>Tools (scores, indices) – inconsistent or poor performance</td>
</tr>
</tbody>
</table>
47. Antoniou et al. 2019  
Abdominal Aortic Aneurysm  
7  1,440  degenerative loss of skeletal muscle  
"Patients with low skeletal muscle mass had a significantly higher hazard of mortality than those without low skeletal muscle mass (HR 1.66, 95% CI 1.15-2.40; p = .007). Subgroup analysis including only patients who underwent EVAR showed a marginal survival benefit for patients without low skeletal muscle mass (HR 1.86, 95% CI 1.00-3.43; p = .05). Meta-analysis of two studies found no significant difference in peri-operative mortality (RD 0.04, 95% CI -0.13 to 0.21) and morbidity (OR 1.58, 95% CI 0.90-2.76; p = .11) between patients with and without low skeletal muscle mass.  
CONCLUSION: There is a significant link between low skeletal muscle mass and mortality in patients undergoing AAA repair. Prospective studies validating the use of body composition for risk prediction after aortic surgery are required before this tool can be used to support decision making and patient selection."

48. Cao et al. 2019  
Cervical cancer  
19  6521  pretreatment thrombocytosis  
"The summary results indicated that an elevated platelet count was significantly associated with a poor OS (HR 1.50; 95% CI 1.19-1.88; P = 0.001), PFS (HR 1.33; 95% CI 1.07-1.64; P = 0.010), and RFS (HR 1.66; 95% CI 1.20-2.28; P = 0.002). Sensitivity analysis indicated that the pooled PFS was variable after sequential exclusion of individual studies. The predictive value of pretreatment thrombocytosis on OS differed according to the publication year (P = 0.039), country (P =

<table>
<thead>
<tr>
<th>49. Feng Q et al. 2019</th>
<th>Primary gastric cancer</th>
<th>101 model developments and 32 external validations</th>
<th>Models for predicting overall survival</th>
<th>&quot;The median (range) of training sample size, number of death, and number of final predictors were 360 (29 to 15320), 193 (14 to 9560), and 5 (2 to 53), respectively. Ninety-one models were developed from routine clinical data. Statistical assumptions were reported to be checked in only nine models. Most model developments (94/101) used complete-case analysis. Discrimination and calibration were not reported in 33 and 55 models, respectively. The majority of models (81/101) have never been externally validated. None of the models have been evaluated regarding clinical impact.&quot;</th>
<th>Most models not suitable for clinical use; further validation/updating required</th>
</tr>
</thead>
<tbody>
<tr>
<td>50. Feng W et al. 2019</td>
<td>patients with metastatic colorectal cancer receiving bevacizumab as first-line chemotherapy</td>
<td>7</td>
<td>1,219</td>
<td>serum lactate dehydrogenase (LDH) level</td>
<td>&quot;Meta-analysis of all studies revealed that high serum LDH level is associated with shorter PFS (HR: 1.43, 95% CI: 1.05-1.94; P=0.023) and OS (HR: 1.667, 95% CI: 1.230-2.259; P=0.001) times in mCRC patients treated with bevacizumab-based first-line chemotherapy. However, there was no significant association between serum LDH and objective response rate. Conclusions: High serum LDH level is significantly associated with shorter PFS and OS time and may have utility as a prognostic factor for mCRC patients receiving bevacizumab as first-line chemotherapy and as a predictive Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed</td>
</tr>
<tr>
<td>Study</td>
<td>Type of Event</td>
<td>Pre-arrest factors associated with reduced odds of survival after in-hospital cardiac arrest:</td>
<td></td>
<td></td>
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<td>------------------------------------------------------------------------------------------</td>
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</table>
| 51. Fernando et al. 2019 | in-hospital cardiac arrest | - male sex (odds ratio 0.84, 95% confidence interval 0.73 to 0.95, moderate certainty),  
- age 60 or older (0.50, 0.40 to 0.62, low certainty),  
- active malignancy (0.57, 0.45 to 0.71, high certainty),  
- history of chronic kidney disease (0.56, 0.40 to 0.78, high certainty) |

Intra-arrest factors associated with increased odds of survival:
- witnessed arrest (2.71, 2.17 to 3.38, high certainty),  
- monitored arrest (2.23, 1.41 to 3.52, high certainty),  
- arrest during daytime hours (1.41, 1.20 to 1.66, high certainty),  
- initial shockable rhythm (5.28, 3.78 to 7.39, high certainty).

Intra-arrest factors associated with reduced odds of survival:
- intubation during arrest (0.54, 0.42 to 0.70, moderate certainty)
- duration of resuscitation of at least 15 minutes (0.12, 0.07 to 0.19, high certainty).

52. Glasmacher et al. 2019

| c9orf72RE disorders, including amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) |
|---|---|---|
| 206 | 1060 |
| prognostic factors in c9ALS, c9FTD, c9ALS-FTD, and atypical phenotypes |

“The median (95% CI) survival (in years) differed significantly between patients with c9ALS (2.8 [2.67-3.00]), c9FTD (9.0 [8.09-9.91]), and c9ALS-FTD (3.0 [2.73-3.27]); survival in atypical phenotypes varied substantially. Older age at onset was associated with shorter survival in c9ALS (HR, 1.03; 95% CI, 1.02-1.04; P < .001), c9FTD (HR, 1.04; 95% CI, 1.02-1.06; P < .001), and c9ALS-FTD (HR, 1.02; 95% CI, 1.004-1.04; P = .016). Bulbar onset was associated with shorter survival in c9ALS (HR, 1.64; 95% CI, 1.27-2.08; P < .001). Age at onset and bulbar onset ALS remained significant in multivariable regression including variables indicating potential diagnostic ascertainment bias, selection bias, and reporting bias. Family history, sex, study continent, FTD subtype, or the presence of additional pathogenic sequence variants were not significantly associated with survival. Clinical phenotypes in patients with neuropathologically confirmed frontotemporal lobar degeneration-TDP-43, motor neuron disease-TDP-43 and frontotemporal lobar degeneration-motor neuron disease-TDP-43 were heterogenous and impacted on survival.”

53. Graizel et al. 2019

| oral squamous cell carcinoma |
|---|---|---|
| 11 | 1040 |
| cancer-associated fibroblasts (CAFs) |

"Univariate Cox regressions showed that high CAF density was a negative prognostic factor in Single marker (i.e. relative"

Prognostic/predictive value of small set of parameters confirmed, highly specific context of condition and/or therapy

| 54. He et al. 2019 | colorectal cancer with surgical resection | 83 original prediction models and 52 separate external validation studies were identified | Prediction models | “We identified five models (Basingstoke score, Fong score, Nordinger score, Peritoneal Surface Disease Severity Score and Valentini nomogram) that were validated in at least two external datasets with a median summarized C-statistic of 0.67 (range: 0.57-0.74). These models can potentially assist clinical decision-making. Besides developing new models, future research should also focus on validating existing prediction models and investigating their real-world impact and cost-effectiveness for CRC prognosis in clinical practice.” | Most models not suitable for clinical use; further validation/updating required |
| 55. Jiang et al. 2019 | non-small cell lung cancer (NSCLC) | 10? (abstract ambiguous) | circulating tumor cells (CTCs) prior to initial treatment | “Randomized model analyzing multivariate Cox Proportional Hazards Regression indicated that higher abundance of CTCs significantly predicts poorer prognosis of lung cancer cases basing | Single marker (i.e. relative importance unclear),
both on PFS (Z = 2.31, P = 0.02) and OS of advanced cases (Z = 2.44, P = 0.01), and systematic study also indicated the similar results.

CONCLUSION: High CTCs prior to initial treatment can predict shorter PFS and OS in NSCLC, and further studies are warranted in the future.

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Cancer Type</th>
<th>Sample Size</th>
<th>Marker</th>
<th>Prognostic/Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>56. Li S et al. 2019</td>
<td>Breast cancer</td>
<td>19, 12,505</td>
<td>programmed cell death ligand-1 expression</td>
<td>PD-L1 expression was significantly associated with lymph node metastasis (P &lt; .001), high tumor grade (P &lt; .001), negative hormone receptor (P &lt; .001), human epidermal growth factor receptor 2 (HER2) positivity (P &lt; .001), high Ki67 (P &lt; .001), and high tumor-infiltrating lymphocytes (TILs) (P &lt; .001). PD-L1 expression had no significant impact on CSS (pooled HR 0.83, 95% CI = 0.64-1.09, P = .19) or MFS (pooled HR 1.11, 95% CI = 0.62-1.97, P = .72), but significantly correlated with shortened OS (pooled HR 1.52, 95% CI = 1.14-2.03, P = .004) and DFS (pooled HR 1.31, 95% CI = 1.14-1.51, P &lt; .000). Subgroup analysis showed that not PD-L1 RNA expression, but protein expression was associated with shorter survival, in addition, the adverse prognostic effect of PD-L1 expression remained in luminal A, luminal B, and HER2 subtype, not in basal-like or triple-negative subtype.</td>
</tr>
<tr>
<td>57. Li W et al. 2019</td>
<td>Brain metastasis in non-small cell lung cancer</td>
<td>18, 4373</td>
<td>mutation of the epidermal growth factor receptor (EGFR)</td>
<td>Mutated EGFR associated with significantly improved OS compared with wild type. Subgroup analyses suggested that this relationship persisted in studies conducted in Eastern, with retrospective design, with sample size &gt;=500, mean age of patients &gt;=65.0 years, Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of cancer</th>
<th>Number of studies</th>
<th>Methodology</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mierzynska et al. 2019</td>
<td>Cancer</td>
<td>44</td>
<td>Baseline patient-reported outcomes (PROs)</td>
<td>Of the 44 studies published between 2006 and 2018 that were included in our review, more standardisation and rigour of the methods used for prognostic factor analysis was found compared with the previous review. 41 (93%) of the trials reported at least one PRO domain as independently prognostic. The most common significant prognostic factors reported were physical functioning (17 [39%] studies) and global health or quality of life (15 [34%] studies). These findings highlight the value of PROs as prognostic or stratification factors in research across most types of cancer.</td>
</tr>
<tr>
<td>Pergialiotis et al. 2019</td>
<td>Ovarian cancer</td>
<td>11 (5 in meta-analysis)</td>
<td>Prechemotherapy hemoglobin (Hgb) levels</td>
<td>Compared with patients with anemia, patients with Hgb levels &gt;12 g/dL had increased odds of overall survival (odds ratio, 1.72; 95% confidence interval: 1.41, 2.10). Current evidence suggests that prechemotherapy Hgb levels below the threshold of 12 g/dL can potentially predict worse overall survival of OC patients. Future research is required in the field to elucidate single marker (i.e. relative importance unclear), prognostic/predictive value confirmed, further research recommended.</td>
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</table>
whether several independent variables such as the stage and histology of disease and rates of optimal debulking affect the clinical significance of this association.”

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Disease Type</th>
<th>N</th>
<th>miRNA Type</th>
<th>Outcome</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>60. Rutherford et al. 2019</td>
<td>colorectal cancer (CRC)</td>
<td>27</td>
<td>12,544 (unclear from abstract if refers to all 27 or the 25 studies which find association with survival)</td>
<td>Patient-reported outcomes</td>
<td>In 25 of 27 studies (n = 12,544), at least one PRO was significantly associated with survival. Physical functioning, fatigue, pain and appetite loss predicted OS more often than other PROs in metastatic disease (19/27 studies). One study explored PRO predictors in early-stage CRC, finding emotional well-being and mood predicted OS. In mixed-stage samples (7/27 studies), physical functioning predicted OS more often than other PROs.” “Physical and psychological functioning, pain, fatigue and appetite loss had prognostic significance above and beyond clinical predictors in CRC.”</td>
</tr>
<tr>
<td>61. Sabarimurugan et al. 2019</td>
<td>Nasopharyngeal cancer (NPC)</td>
<td>21</td>
<td>5069</td>
<td>miRNAs</td>
<td>“The forest plot was generated using cumulated survival data, resulting in a pooled HR value of 1.196 (95% CI: 0.893-1.601) indicating that the upregulated miRNAs increased the likelihood of death of NPC patients by 19%.” “[T]he combined effect estimate of HR across multiple studies indicated that increased miRNA expression in NPC potentially leads to poor overall survival. However, further large-scale prospective studies on the clinical significance of the miRNAs, with sizable cohorts are necessary in order to obtain conclusive results.”</td>
</tr>
<tr>
<td>Reference</td>
<td>Primary Disease</td>
<td>Study Population</td>
<td>Sample Size</td>
<td>Marker</td>
<td>Prognostic Value</td>
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<td>-----------</td>
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<tr>
<td>Sun et al. 2019</td>
<td>Colorectal cancer</td>
<td>10</td>
<td>6372</td>
<td>preoperative prognostic nutritional index (PNI)</td>
<td>“Our overall analysis indicated that the low-PNI group had a significantly reduced overall survival (OS) (HR = 1.87, 95% CI = 1.45-2.42, P &lt; 0.01), cancer-specific survival (HR = 1.53, 95% CI = 1.07-2.19, P = 0.02), and disease-free survival (HR = 1.67, 95% CI = 1.23-2.26, P &lt; 0.01) compared with the high-PNI group. Furthermore, our subgroup results indicated that a high PNI could be a significant indicator of improved OS in TNM stage II (HR = 1.93, 95% CI = 1.29-2.90, P &lt; 0.01) and III (HR = 1.71, 95% CI = 1.25-2.34, P &lt; 0.01), and a similar trend in TNM stage I or IV could also be observed though without statistical significance. Regarding postoperative complications, our pooled results indicated that the low-PNI group had a significantly increased incidence of total and severe postoperative complications. CONCLUSIONS: Our findings indicated that CRC patients with a preoperative high PNI had a significantly improved OS. However, almost only Asian CRC patients were included based on current issue.”</td>
</tr>
<tr>
<td>Wang M et al. 2019</td>
<td>Cancer</td>
<td>6</td>
<td>1584</td>
<td>TRIM59</td>
<td>“The results showed that high levels of TRIM59 were significantly associated with poor OS in cancer patients (HR = 1.43, 95%CI: 1.24-1.66, P &lt; .001), indicating that higher TRIM59 expression could be an independent prognostic factor for poor survival in cancer patients. CONCLUSION: Our meta-analysis suggests that higher TRIM59 expression predicts poor prognosis in cancer patients, and it may therefore serve as a promising prognostic factor.”</td>
</tr>
<tr>
<td>No.</td>
<td>Authors</td>
<td>Study Type</td>
<td>Sample Size</td>
<td>Follow-up</td>
<td>Prognostic Factors</td>
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<tr>
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<tr>
<td>64.</td>
<td>Wang SJ et al. 2019</td>
<td>Repeat hepatectomy for recurrent colorectal liver metastasis (CRLM)</td>
<td>34</td>
<td>3039</td>
<td>Prognostic factors as identified in the literature</td>
</tr>
<tr>
<td>65.</td>
<td>Wang X and Wang Y, 2019</td>
<td>Gynaecological cancer</td>
<td>9</td>
<td>2373</td>
<td>Prognostic nutritional index (PNI)</td>
</tr>
<tr>
<td>66.</td>
<td>Yang C et al. 2019</td>
<td>Patients with malignant solid tumors</td>
<td>17</td>
<td>2,228</td>
<td>T-cell lymphoma invasion and</td>
</tr>
<tr>
<td>Study</td>
<td>Tissue Type</td>
<td>Sample Size</td>
<td>Biomarker</td>
<td>Effect Measure</td>
<td>Conclusion</td>
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</tr>
<tr>
<td>67. Yang L et al. 2019</td>
<td>Nasopharyngeal carcinoma (NPC)</td>
<td>21</td>
<td>Excision repair cross-complementation group 1 (ERCC1)</td>
<td>High/Positive expression (OR = 2.83; 95% CI: 2.11-3.80; P &lt; 0.001)</td>
<td>ERCC1 as a potential predictive and prognostic biomarker for the treatment response and survival prognosis of NPC patients.</td>
</tr>
<tr>
<td>68. Yang M et al. 2019</td>
<td>Lung cancer</td>
<td>13</td>
<td>Sarcopenia (skeletal muscle depletion)</td>
<td>Pooled prevalence of sarcopenia was 43% in patients with non-small cell lung cancer (NSCLC) and 52% in patients with small cell lung cancer (SCLC). Sarcopenia was associated with</td>
<td></td>
</tr>
<tr>
<td>Ref.</td>
<td>Disease</td>
<td>Cases</td>
<td>Controls</td>
<td>Markers</td>
<td>Findings</td>
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<tr>
<td>69. Yu et al. 2019</td>
<td>Liver failure</td>
<td>13</td>
<td>2071</td>
<td>Hepatic encephalopathy</td>
<td>&quot;The results proved the prognostic value of hepatic encephalopathy for survival of patients with liver failure (OR=5.62, 95% CI 6.30-9.82, P&lt;0.001). The subgroup analyses showed that the type of liver failure and the follow up duration may be the factor influencing the association between hepatic encephalopathy and survival of patients with liver failure.&quot;</td>
</tr>
<tr>
<td>70. Cao et al. 2020</td>
<td>Gastric cancer</td>
<td>28</td>
<td>15,617</td>
<td>Platelet-to-lymphocyte ratio (PLR)</td>
<td>&quot;The pooled results indicated that elevated PLR was associated with poor OS (HR: 1.37; 95% CI: 1.24-1.51; P &lt; 0.001). A significant publication bias was observed (Egger test, P = 0.03; Begg test, P = 0.017). After adjusting for publication bias using the trim and fill method, an adjusted pooled HR of 1.19 (95% CI: 1.08-1.33; P = 0.001) was observed. Subgroup analyses indicated an elevated PLR in retrospective studies. Studies conducted in Turkey, the UK, the USA, and...&quot;</td>
</tr>
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</table>
Costa Rica; studies with a sample size of < 1000, with < 70% male patients, and with patients treated with chemotherapy; studies with PLR cutoff value of >=200; and studies with lower quality as determined by the Newcastle-Ottawa Scale all showed greater harmful effects on OS than their corresponding subsets (P < 0.05).

CONCLUSIONS: An elevated PLR was associated with poor OS in patients with gastric cancer. These results might differ between studies due to differences in design, country of origin, sample size, sex proportion, treatment strategy, PLR cutoff value, and study quality.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Sample Size</th>
<th>5-year OS</th>
<th>PNI</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhao et al. 2020</td>
<td>Gastric cancer</td>
<td>7004</td>
<td>Perineural invasion</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

There were significant relationships between PNI and a series of unfavourable clinicopathological factors including undifferentiated histology type (OR: 1.78, 95% CI 1.37 to 2.33, p<0.001; I²=75.3%), diffuse type (OR: 1.96, 95% CI 1.07 to 3.60, p=0.029; I²=79.5%), lymphatic invasion (OR: 7.00, 95% CI 3.76 to 13.03, p<0.001; I²=83.6%), vascular invasion (OR: 5.79, 95% CI 1.59 to 21.13, p=0.008; I²=95.8%), deeper tumour invasion (OR: 4.79, 95% CI 3.65 to 6.28, p<0.001; I²=65.0%) and lymph node metastasis (OR: 3.60, 95% CI 2.37 to 5.47, p<0.001; I²=89.6%). In addition, PNI was significantly associated with worse survival outcome in GC patients (HR: 1.69, 95% CI 1.38 to 2.06, p<0.001; I²=71.0%).
Appendix 1: Further detail on realism and realist reviews

Box 1: More on realism

1a. Realism, in the intellectual tradition of Pawson and Tilley, is characterised by the following assumptions*:

1) Both the material and social words are “real”; anything that can have real effects is real – crucially, this claim is intended to take a stance on the traditionally controversial reality of constructs and entities such as culture, gender, social class, programmes, policies, social institutions, ideas, etc.

2) Mind-independent and interdependent reality – both the natural and social world exist and exert their powers independently of our understanding, judgements and interpretations of them, but they are also affected by human actions based on the latter (in this sense, have a reality interdependent with our ideas).

3) All enquiry and observations are “filtered through” the human mind; therefore, there is no “final” truth or knowledge. However, we can still work towards a closer understanding of reality because reality constraints our interpretations and we can continuously test, judge and refine them.

4) All social systems are open systems – social systems interact and influence one another and change over time, producing outcomes with or without the introduction of a policy or programme. A realist study can only show that a policy or a programme contributed to an outcome.

5) Realism subscribes to a “generative” view of causality (Bhaskar, 1975, Pawson, 2008) in the sense that, briefly, observable outcomes are generated by largely non-observable causal processes and forces (mechanisms), which operate or not depending on the contexts in which they occur. As a result, outcomes vary across different contexts. Realist research aims to identify the mechanisms which cause outcomes, not just associations between programmes and outcomes.

6) Whether mechanisms generate outcomes depends on the context in which they function – realist research identifies what it is about the context that determines whether, and which, mechanisms “fire”.

7) Mechanisms operating in different contexts generate different outcomes – programmes thus generate different outcomes for different groups of people in different contexts, with realist research aiming to identify and explain different outcome patterns.


Box 1: More on realism, continued

1b. Other “realisms” and other realist philosophies of science

While versions of the positions described in 1a. are standard in the realist research community circumscribed as above, such an interpretation of realism becomes problematic, or at least too facile, when mapped against debates on realism (including distinctions between realism about the world and realism in the philosophy of science), causality, mechanisms, explanation, theories, etc. in “hard-core” philosophy communities, especially if these are part of the philosophy establishment as opposed to the social sciences one.

From the perspective of a broader understanding of philosophical realism, realist research in the Pawson, Tilley and RAMESES tradition has appropriated a name belonging to a much more varied set of conceptualisations and endeavours. The specificity of its understanding of concepts such as causation, mechanisms, theory and explanation, amongst others, while necessary and expected, can also cross into the parochial, contributing to a level of “realist group think” which outsiders to the intellectual community or even critical insiders may, at times, experience.

It is, however, an open question whether a methodological debate which is better embedded in a broader understanding of philosophical realism and/or more varied (realist) perspectives from the philosophy of science around causation, mechanisms, theories, etc. will change substantively, or even at all, the way the applied work is conducted.

1c. Realist synthesis in the context of other “alternative” synthesis methods

Realist reviews are one of a significant number of approaches developed in the 1990s / early 2000s in response to limitations of the mainstream, Cochrane type, systematic reviews.[22] These approaches seek to open up space for meaning-making, explanation, interpretation and theory; a broader understanding of evidence; a greater procedural flexibility; and opportunities for handling significant complexity in an endeavour that has become too self-limiting, largely by virtue of its narrow focus on evidence (or a focus on evidence, narrowly understood).

Basic bibliometric searches in PubMed covering the last five years suggest that out of 29 methodological alternatives to the mainstream systematic review and/or a narrative summary/ synthesis,[22] realist synthesis is amongst the four most widely used methods, alongside thematic synthesis, content synthesis and qualitative meta-synthesis (372 papers retrieved by “realist review” OR “realist synthesis”, Sep 2020).

Main advantages of the realist approach we perceived relative to pertinent alternatives were:

1) its focus on programmes as a key unit of analysis (with many interventions in palliative and end of life care in primary care and the community taking such a form);
2) the disciplined, “obligatory” way in which contextual influences are traced, through every CMO-configuration formulated (with outcome patterns in palliative and end of life care characterised by dramatic variations across contexts);
3) its openness to an exceptionally broad variety of evidence (accommodating the endless variety of perspectives that can be taken towards death and dying outside of palliative and end of life care);
4) its commitment to broad stakeholder involvement, including policy makers, practitioners, programme participants and the public, which acknowledges the value of each perspective, the privileged status of some perspectives relative to some questions but, at the same time, does not ascribe ultimate authority to any stakeholder group.
Table 1: Some strengths and weaknesses of a realist review from the perspective of an exemplar (Cochrane-type) systematic review

This table outlines key differences between a realist review and an exemplar (Cochrane-type) systematic review in terms of the research question, inclusion and exclusion criteria, and approach to literature searching. It is not an exhaustive comparison of the methods but, rather, focuses on challenges raised by initial reviewers of this paper. The last column summarises the steps we have taken to “bridge the gap”, i.e. improve on features of the realist review which are likely to be perceived as limitations or even failures in comparison to a mainstream systematic review. The steps taken are relatively unusual in the realist synthesis literature but, we argue, consistent with the spirit and methodological injunctions of the approach.

<table>
<thead>
<tr>
<th>Key element of a review</th>
<th>The realist approach</th>
<th>Strengths relative to the traditional (Cochrane-type) systematic review</th>
<th>Weaknesses from the perspective of the traditional systematic review</th>
<th>Strategy used in this review to bridge the gap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research question/ review focus</td>
<td>The initial research question can be quite broad, as it is typically generated by real-life practical concerns and policy needs as opposed to arising in a research context. It also tends to concern complex social programmes rather than discrete treatments such as new drugs. The review focus tends to become narrower as the study progresses.</td>
<td>The review questions asked are closer to the actual questions asked in complex policy and practice contexts. The work on focusing the review is highly responsive to new cues in the data, which could not have been anticipated at the start of the study.</td>
<td>The initial review questions may appear unspecific, possibly challenged as unanswerable in a scientific way. The process of focusing the review may appear to be changing what the review set out to achieve and, as such, to be compromising the integrity of the study.</td>
<td>We used a robust stepwise approach, involving 12 key stages, of making the transitions from the original to the final review questions. We still provided a high-level answer to some of the original review questions through the working typology of programmes in palliative and end of life care in primary care and the community.</td>
</tr>
</tbody>
</table>

2 The process of focusing the review involved the following stages described in the paper: 1. developing a realist typology of programmes for palliative and end of life care; 2. identifying a key theme within the typology which met five criteria (see paper for criteria). The time and timing theme was decided upon as a tentative focus; 3. test coding for CMO configurations on time and timing; 4. extensive team discussion. The other main candidate theme for a narrower review focus was “carers” The focus on identification within the time and timing theme was decided upon through the following stages: 6. We identified themes related to time and timing in palliative and end of life care using all papers in the main dataset; 7. coded influential UK policy documents on palliative and end of life care for themes related to time and timing; 8. identified the intersections between themes in the research literature and themes in the policy documents (four key themes); 9. developed CMO configurations for all four themes; 10. conducted targeted searches on two of the themes and developed further CMO configurations based on them; 11. consulted stakeholders (the professionals’ Advisory Group and the PPI Group) on the emergent findings. 12. finalised the review focus on timely identification of the dying phase and timely initiation of palliative and end of life care services.

### Key element of a review

<table>
<thead>
<tr>
<th>Research question/ review focus, cont.</th>
<th>Inclusion/exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>The realist approach</strong></td>
<td><strong>Studies or parts of studies are included in the review depending on the degree to which they illuminate an emerging theory.</strong></td>
</tr>
<tr>
<td><strong>Strengths relative to the traditional (Cochrane-type) systematic review</strong></td>
<td><strong>The strong explanatory aspect of a realist review, systematically supported by data, allows programme developers, practitioners and policy makers to make sense of patterns they know from experience and discern new ones. In turn, they can devise or refine programmes on the basis of “theories” (theories of change, logic models, lines of argumentation, etc.) as opposed to being confronted by piecemeal evidence which rarely speaks for itself.</strong></td>
</tr>
<tr>
<td><strong>Weaknesses from the perspective of the traditional systematic review</strong></td>
<td><strong>Inclusion/exclusion criteria can appear vague. Explanations may be brought in from other areas creating a potential sense of confusion about the scope of the study. As typical inclusion/exclusion criteria such as health condition, setting, age group, etc. correspond to factors which may or may not play a role in theoretical explanations, fundamental features of the review, such as its target.</strong></td>
</tr>
<tr>
<td><strong>Strategy used in this review to bridge the gap</strong></td>
<td><strong>Provided a detailed analysis table (Appendix 5) to demonstrate the logic of the derivations. Provided conceptual detail and numerical data on the 9 &quot;levels of relevance&quot; into which we classified studies (Appendix 4 on Literature searching).</strong></td>
</tr>
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</table>

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## Key element of a review

<table>
<thead>
<tr>
<th>The realist approach</th>
<th>Strengths relative to the traditional (Cochrane-type) systematic review</th>
<th>Weaknesses from the perspective of the traditional systematic review</th>
<th>Strategy used in this review to bridge the gap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion/ exclusion criteria, cont.</td>
<td></td>
<td>population, setting, even overall topic, may seem to shift. Searches that deliberately (with good justification) reach outside the programme under study (and thus create a worse version of the limitations above) are considered a feature of an excellent review within the realist approach.</td>
<td></td>
</tr>
<tr>
<td>Search strategy</td>
<td>Aims to identify sources rich in explanatory detail and evidence that can confirm or reject emerging hypotheses rather than the totality of relevant evidence. Develops iteratively, with targeted searches decided upon as the emerging theory is fleshed out.</td>
<td>Responsive to growing understanding of the topic of interest. As the explanations at the lower levels may include concepts different to those in the review questions, the searches may appear insufficiently matched to the review questions.</td>
<td>Transparency about the search strategy and indication of the topics of all targeted searches, even if, ultimately, not used (Appendix 4 on Literature searching).</td>
</tr>
</tbody>
</table>

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Appendix 2: Diagrammatic representation of rough programme theories, as developed at the outset of the study
Accompanies: Petrova, Wong, Kuhn, Wellwood and Barclay, “Dying and time”

Programmes, initiatives, tools, activities ...

EoLC patient identification approaches and tools
- “Surprise question”
- Structured prediction tools (examples?)
- GSF register

Approaches and tools for eliciting and recording care preferences (in the context of sensitive conversations) and developing a care plan around them
- GSF
- PPC (Preferred Priorities for Care)
- EPaCCS (Electronic Palliative Care Coordination Systems)
- service-specific care planning tools
- legalistic approaches and tools (e.g. ADRT, power of attorney)

Training
- In having sensitive/ difficult conversations
- Recognising signs of dying
- Using the structured tools

Incentives
- E.g. QOF for GSF register, CQUINS, 1% and 2% LES and DES

Supportive context
Greater overall investment in and attention to end of life care
Local and national incentives for identifying EoLC patients, discussing their care preferences and preparing care plans
More open social conversation on death and dying

High quality EoLC starts with
- Timely identification of EoLC patients
- Elicitation and recording of their care preferences
- The preparation of a care plan on the basis of those preferences

Underpinning assumptions/mechanisms:
As ~ 70% of deaths are predictable, timely identification is possible for the majority of patients. It needs to be enabled by the appropriate and consistent provision of awareness raising activities, training and tools.

High quality end of life care meets a patient’s individual preferences. These need to be identified through sensitive conversations, and adequately recorded and updated.

Lack of skills and confidence amongst health professionals in discussing death and dying is a main barrier. Improving training provision is key.

Progress with the identification and management of cancer patients has been significant. We need to focus on other conditions and also address other sources of inequality.
Appendix 2: Diagrammatic representation of rough programme theories, as developed at the outset of the study
Accompanies: Petrova, Wong, Kuhn, Wellwood and Barclay, “Dying and time”

Countervailing mechanisms

Prognosis is not that straightforward
- The disease trajectory for conditions other than cancer is far less predictable
- Research evidence suggests that predictions in EoLC are frequently inaccurate (e.g. White et al. 2016 systematic review)

Sharing a negative prognosis is not value-neutral – the value of maintaining hope may clash with values around truth (which is uncertainly anyway), preparation, freedom of choice and control over one’s life (and death)

Preferences are not fixed – patient preferences are not necessarily well shaped, can be dynamic, change on the basis of services available, etc.

Elicitation of preferences is complex
Having sensitive EoLC conversations cannot be taught in a 2-hour training session
This is not a conversation that fits in a 10-min appointment
Trust and the quality of the relationship with a patient are important. You need to have/ build the right relationship to have the conversation.
There is much noise in communication channels in principle, let alone in the case of conversations about death and dying, where euphemisms are often used (i.e. what clinicians have said and what patients have heard can be quite different)

Care planning
Ultimately, you are trying to predict something that is highly unpredictable.
If the services are not available, what you have planned for is totally irrelevant. It is even unethical as it may sound like a promise/ commitment when discussed with patients.

Challenging contexts

Service level
If the services are not available, their availability unpredictable and we are going to do what we are going to do anyway, it is problematic, even unethical to be eliciting preferences.

Patient social context
Patient and his/ her family preferences may differ, and family members are also our patients. We need to consider them too in our planning.

Informational context
Data sharing only happens in pockets, not at all, or using traditional methods of inter-professional communication. We may be identifying and recording preferences and plans in our service, but if colleagues are not aware, much of that effort is wasted.

The identification of EoLC patients, the elicitation and recording of their preferences and the preparation of a care plan are more complex than may appear at first sight
Appendix 2: Diagrammatic representation of rough programme theories, as developed at the outset of the study

Accompanies: Petrova, Wong, Kuhn, Wellwood and Barclay, “Dying and time”

Programmes, initiatives, services, etc.
(in addition to standard practice, e.g. GP and DN visits, care provided by the family)

Home-based services:
- Community palliative care teams
- Hospice@home services
- Rapid response teams
- Paid carers
- Lay volunteers

Provision of equipment for home care

Admission avoidance/hospital stay reduction schemes:
- Better information provision to ambulance staff and A&E through data sharing initiatives
- Fast track discharge
- Palliative care teams which work across the hospital and community
- Training

Support for carers
- Respite
- Training
- Counselling, confidential telephone lines, carer groups, etc.

As most patients prefer to be cared for/die at home, community care is both congruent with patient preferences and more financially sustainable

Supportive context
- Greater investment in community services in general and community EoLC services in particular
- Improvements in the local IT infrastructure (e.g. mobile working, data sharing)
- Compassionate communities

Underlying assumptions/mechanisms
- Home is the place where people feel most at peace, supported, safe and where they will be closest, in their final hours, to the ones who love them.
- Community care is cheaper than hospital care.
- Busy, open and impersonal hospital spaces can be a traumatic environment to die in and/or witness your loved one die.
- If a patient prefers to be cared for at home (and this information is known and shared appropriately) and if we provide sufficient support at home, hospital admissions at the end of life are, generally, both unwanted and unnecessary.
- There is a growing range of high quality community EoLC services. However, we need to address gaps in provision and sources of inequality.
Appendix 2: Diagrammatic representation of rough programme theories, as developed at the outset of the study

Accompanies: Petrova, Wong, Kuhn, Wellwood and Barclay, “Dying and time”

Countervailing mechanisms

There is a level of idealisation of home as a place of care/ death — e.g. help is not available at the press of a button and pain may be poorly controlled as services are not sufficient; the equipment turns the home into a hospital at home, etc.

Admissions may only appear inappropriate, even if a patient’s core preference is to be cared for/ die at home and even if those preferences are known — e.g. patients and family get scared; carers are exhausted; community services to keep the patient at home are not available at the time they are needed and it is safest to take the patient to hospital.

Cost savings do not mean no investment

Good community services cost money, and this often needs to be invested in advance.

There is limited evidence on the overall costs of community services.

Family time is often unaccounted for, and the costs which are thus shifted to families can be significant.

Providing services which meet the complex and dynamic patient preferences and the highest standards of EoLC in the community is fraught with difficulty. The financial advantages of community care are not as definitive as they may seem.

Challenging contexts

Service level

The services which are part of standard practice (e.g. GP and DN involvement) are under so much pressure that an important pillar of community services is not as reliable as assumed.

The provision of EoLC community services is unequal.

Financial context

Funding cuts

Funding arrangements can lead to perverse incentives or disincentives to community care.

Geography

Remote, rural and disadvantaged areas will typically have less community services in place.

Areas which fall at administrative/ team coverage boundaries can fall between two chairs.

Social context

Community EoLC services rely on some level of support from a person’s social network. Not everybody has that.
Appendix 3: Stakeholder involvement

Here we report on the stakeholder involvement in our review using the Short Form of GRIPP2 (Guidance for Reporting Involvement of Patients and the Public) reporting checklist, while adding the Definition and Theoretical underpinnings parameters from the Long Form. Clarification of terminology and background assumptions was needed, as stakeholder involvement in realist research is broader than Patient and Public Involvement (PPI).

GRIPP2 forms as in:


1. Definition

While we did not start from a formal definition of stakeholder involvement, we had extensive team discussions of how to proceed with it and how to optimise it, particularly relative to standard challenges faced by PPI, such as professionalisation or unrepresentativeness of PPI groups. Below is a post-factum articulation of our starting positions:

*Stakeholder involvement is a process whereby non-researchers and non-study participants are consulted with the goal of improving the study relevance; focus; applicability; chances of successful recruitment and retention of participants (or, in a review, the identification of relevant sources); valid analysis; and effective dissemination of findings. It is also a form of ensuring greater accountability and broader social feedback for research, which can become too disconnected from its intended users and beneficiaries and the society which often funds it.*

*More broadly, from the perspective of social inclusion and justice, the patient and public involvement aspect of stakeholder involvement is one of numerous ways in which individuals and social groups which are not in powerful positions can be encouraged to influence social conversations and practices which affect them; develop/refine the knowledge and skills to enable them to do so successfully; and develop the confidence that their views are valuable and that there are ways for them to be heard.*

At the start of the work, our main concerns about PPI involvement were:

1) the tendency for PPI groups to be insufficiently representative of the breadth and substrata within ‘patients and the public’ and to reproduce entrenched social inequalities (e.g. PPI members are often white, middle class, educated, articulate, retired);
2) the tendency for PPI group members to become professionalised (and, arguably, lose some of the novice’s and outsider’s ability to notice and challenge problems and inefficiencies);

3) the degree to which PPI is being advanced as a requirement and unquestionable good in health research (provided it is “done well”, and not in a “tokenistic” way), limiting researchers’ abilities to engage probingly and critically with it without being accused of elitism and paternalism. While being strong supporters of PPI, we do believe the practice needs a far more open and critical debate to which we are aiming to contribute.

In responding to reporting requirements throughout the study (including in using the GRIPP checklists here, which address PPI involvement), we had to manage an ambiguity characteristic of realist methods and other methods relying on broad stakeholder engagement and involvement. “Stakeholders” in such contexts includes not only patients and the public, but also professionals, policy makers, commissioners, etc. Moreover, no type of stakeholder in a realist study is, by default, privileged or more important than any other type of stakeholder. Different types of stakeholders are likely to have experience with, be sensitive to and ‘see’ different aspects of the big picture needed for the study.

Furthermore, as the involvement of professional stakeholders in research is typically structured around the needs of the study and the culture of research as opposed to the practices, rules, norms, etc. constituting a professional role (e.g. a health professional is a professional but outside of their field of practice), a professional stakeholder can also provide input ‘simply’ as a patient and member of the public.

It is an interesting and, we believe, open question if patients and the public should be the ‘privileged’ stakeholders (as having a reporting checklist only for this stakeholder group seems to imply). The question is particularly relevant in the case of research whose recommendations can be acted on first and foremost by health professionals, policy makers, commissioners, service developers, etc., even if its ultimate beneficiaries are intended to be patients and the broader society.

2. Theoretical underpinnings

Our literature review was conducted within a realist framework, as described in sources such as Pawson and Tilley (1997), Pawson (2002 a,b), Wong et al. (2013) and The RAMESES Project (2014). In realist studies, stakeholders with knowledge of a programme (intervention) are involved in ways that enable a researcher to put to test, and as a result confirm, falsify and refine, a theory about the programme’s workings. Expertise (and inexpertise) concerning a programme theory varies from aspect to aspect of a problem and from one programme to another (Pawson and Tilley, 1997; p.159-160).

Tentatively, it can be expected that programme subjects (e.g. patients in a healthcare context) will be more sensitized to the mechanisms in operation within a programme rather than to its contextual
constraints and outcome patterns (op. cit., p. 160). As mechanisms, within a realist framework, provide reasons and resources encouraging participants to change, patients are well positioned to comment whether this has been effective, albeit most likely presenting a rather personal view of the interaction between programme mechanisms and their (the patient’s) pre-existing capacities (ibid.). Practitioners, in turn, are likely to have specific ideas on the aspects of the programme that make it work; likely to have experienced both successes and failures of it; and to have some awareness of people and places for whom and in which the programme works (op. cit., p. 161). Typically, they have a limited ability to systematise, abstract and generalise from their personal and institutional experience (ibid.).

Evaluators (researchers) are bringing in the theoretical knowledge – CMO-configurations they are familiar with from other programmes and more abstract propositions from social science theories. They are, however, stronger on form than content (op. cit., p. 161).

Each of these stakeholders has something to teach the others and something to learn from them (op. cit., p. 161).

Describing the role of stakeholders in realist studies, as per core methodological texts, is a research question in its own right. In our still evolving understanding, the realist approach does not ascribe a privileged status to patients and the public in comparison to other stakeholders in the research process. In contrast, mainstream PPI thinking, one of whose checklists we are using, appears to adopt such a view.

3. Aims

Relative to the theoretical underpinnings described above, stakeholders are involved in a realist study so as to contribute, with their experience and perspective, to the testing and refinement of a programme theory, which is the study’s main focus and outcome.

4. Methods

4.1. Convening stakeholder groups

Within the core study team, we had several (4-5) extensive discussions about stakeholder involvement and the most effective ways of enabling it.

The Cambridge Palliative and End of Life Care (CPEOLC) Group, which hosted the study, has a long-standing tradition of PPI involvement. However, as key concerns raised in the team discussions had been the downsides of PPI professionalisation and the value of broadening the variety of perspectives we had access to, we decided against approaching the PPI network of the CPEOLC group.

Initially, we engaged with an existing Sustainability and Transformation Partnership (STP) End of Life Care Board, which also has PPI representation, as a form of Advisory Group for the review. This was because all key local (Cambridgeshire & Peterborough) stakeholders in palliative and end of life care...
were already represented there. The original meeting provided us with some useful insights, but we decided to convene a project-specific Advisory Group.

We further approached a pre-existing PPI group, part of an infrastructure established and maintained by the National Institute for Health Research (NIHR) Cambridge Biomedical Research Centre (BRC). Unlike our CPEOLC network of PPI contributors, PPI members on this panel had no specific prior involvement in end of life care research. We assumed this would allow us to tap into less familiar points of view. 8 panel members attended the first meeting (early stages of the review) and 6 the second (towards the end of the review).

We also convened a project-specific Advisory Group using SB’s networks of palliative and end of life care professionals. 16 people expressed interest to join the group, of whom 8 were able to attend the first project meeting and 6 the second meeting. Several group members who could not attend either meeting provided feedback over email.

4.2. Activities

The main mode of engagement with the two stakeholder groups were face-to-face meetings, separate with each group: one meeting with each of the groups in October 2018 and one meeting with each of the groups in November 2019. The main goals of the first set of meetings were to discuss the scope of the review and the emerging rough programme theory. The main goals of the second set of meetings were to receive feedback and solicit reflections on key findings, serving to test further and help us refine the CMO-configurations under development.

Two members of the core research team attended each of the meetings (MP with either SB or IW) with the exception of the second PPI meeting (MP only).

Following the first meeting, we produced a 20-page document that brought together the input of the professionals’ Advisory Group and of the PPI Group. The document covered issues discussed at our original meetings and elicited initial Context-Mechanism-Outcome configurations. We circulated it to both groups with a request for feedback on “missing pieces”, if any, and “priorities within the priorities”. Feedback and additions were minimal, with overall comments that this was an impressive document.

Throughout the project and primarily around meetings with the groups, MP also had email exchanges with stakeholders, enabling further insight into the palliative end of life care-related experiences of patients, carers and health professionals and the workings of current services and programmes.

5. Outcomes of stakeholder involvement

5.1. Impact on the scope of the review

We received important guidance on the scope of the review from both groups. For instance, we were inclined to exclude research on care homes, hospices and day care centres. However, it
became apparent that such settings had been central to both positive and negative experiences of end of life care for members of the PPI Group while accompanying family members in their final days. The hospice representation on the professionals’ Advisory Group also meant the prominence of the setting remained high, while, within the team, we had discussed excluding literature on hospices by virtue of them being “too specialist”, even if community based.

Both meetings with the PPI Group underscored in emotional ways the importance of carers in palliative and end of life care. The research we had been identifying and screening, the policy documents reviewed, and the input of the professionals’ Advisory Group would not have resulted in a similar prominence of the carer perspective. The latter remained a key consideration throughout the data identification, analysis and synthesis stage, both in terms of explanatory models and issues prioritised.

5.2. Contribution to theory development and refinement

The discussions at the inaugural meetings with both groups, and particularly with the professionals’ Advisory Group, contributed significantly to developing the rough programme theory and specifying sub-questions within the broad review questions we had formulated for the study protocol. A detailed document on this contribution is available from the authors. Participants’ experiences, ideas and reflections from those meetings also supported the formulation of CMO-configurations during data analysis.

5.3. Impact on achieving balance

The second PPI meeting was exceptionally helpful in highlighting, in rather emotional ways at times, that a significant proportion of patients and carers do not receive palliative and end of life care at all. In view of their, at times, excruciating experiences, members of the PPI Panel intensely disagreed with some of our criticisms of a policy overemphasising identification of the end of life stage. The strong reaction against some of our evidence-based claims alerted us to the importance of careful framing and of fairness to the more conventional perspective, which should not be undermined, only expanded.

5.4. Impact on motivation and accountability

We experienced both forms of stakeholder involvement as very motivating in conducting the review. We felt encouraged to proceed with it and more confident in its importance and relevance.

We also had clear reminders that we need to give sufficient priority to the dissemination of findings and target dissemination efforts at a variety of primary audiences.

6. Discussion and conclusions

The involvement of both stakeholder groups was key to the direction of the study, as the specific outcomes above demonstrate.
7. Reflections/critical perspective

7.1. Representativeness and fluctuations of membership

Even though we sought an external PPI group (external to the Cambridge Palliative and End of Life Care research group) which could draw on a much larger pool of potential participants, the group was still insufficiently representative of the broader public.

It was also inconsistent in membership, with three new members and a new coordinator attending the second meeting. As a result, we needed to re-introduce the project and make space for the palliative and end of life care experiences that have brought each of the panel members (and us) to the meeting. Creating the right emotional environment is crucial for PPI involvement in palliative and end of life care research. However, in new groups or groups with significant fluctuations of membership, it may mean that the substantive work moves to the background for the better part of a meeting.

7.2. Expectations

In a literature review, the shape of the study is strongly determined by the available literature. There is a risk that the particularities of the available research, together with the need to focus the review further and further from its initial ambitions, creates, at the end of a study, the impression that the research team have taken very little of the contribution of stakeholders on board.

Our second PPI meeting also made us wonder if PPI groups are not almost exclusively consulted at the beginning of a study, making a meeting focusing on sense checking and refining findings unexpected and, by extension, requiring a much more detailed introduction. We found the meeting in question exceptionally helpful, yet in a diffuse way (see 5.3. Impact on achieving balance), almost unrelated to the specifics of our findings (which were discussed in much greater detail with the professionals’ Advisory Group). The findings moved to the background, as it felt far more important to open up space to discuss the issues that were coming up in the PPI Group there and then. Perhaps the Panel perceived their role as giving initial input on relevant issues, while the research team (represented by MP) was hoping to obtain feedback on highly specific and already formulated findings. Extra care may be needed in preparing and introducing such meetings, making clear they are “different” to normal PPI meetings.

7.3. Professionalisation – a revised perspective

A key challenge of PPI involvement we discussed at team meetings early on in the study was the level of professionalisation in PPI, including in the PPI Group associated with the Cambridge Palliative and End of Life Care Group – a group we had direct access to but decided not to approach for the purposes of this study. With the benefit of hindsight, we see many more of the advantages of such professionalisation. The iterativity of participation allows for the development of long-standing relationships between researchers and PPI representatives, and amongst the PPI representatives themselves. This, in turn, contributes to a safe, trusting environment which is key in palliative and...
end of life care research. Repeated participation also allows for the clarification of roles and expectations and for ongoing, both formal and informal, training in research methods.

We would like to thank sincerely all stakeholders who contributed to this study.

REFERENCES:

Appendix 4: Approach to searching and screening the literature

1. Generating the main dataset

The scope, databases and keywords for the literature searches were discussed from the start of the project, in the context of its regular team meetings, by IK (library and information specialist), MP (lead researcher, domain expert – palliative and end of life care), IW (systematic reviews expert), GW (realist methods expert and domain expert – general practice), SB (domain expert – palliative and end of life care and general practice). IK then designed test searches, whose contents and retrieval were reviewed by MP. Minor modifications were introduced. This work generated the main search strategy for the review. It combined four blocks of search terms around:

- palliative and end of life care;
- primary and community care;
- United Kingdom, using the filter for Medline by Ayiku et al.¹ and adapting it for other databases;
- programme (theory, model, philosophy).

Eight databases were searched from 1990 onwards, with the search run on 24th April 2018:

- Medline via OVID
- Embase via OVID
- CINAHL via EbscoHost
- PsycINFO via EbscoHost
- Web of Science
- ASSIA via ProQuest
- Sociological Abstracts via ProQuest
- SCIE Social Care Online

¹ Ayiku L, Levay P, Hudson T, Craven J, Barrett E, Finnegan A, Adams R. The MEDLINE UK filter: development and validation of a geographic search filter to retrieve research about the UK from OVID MEDLINE. Health Info Libr J. DOI: 10.1111/hir.12187
The complete search strategy for each of the databases is presented at the end of this document, under **Main search, version 3**.

The main search generated a deduplicated dataset of 3039 citations.

Subsequently, records between 1990 and 1997 were removed after a decision to use the 2008 End of Life Care Strategy for England\(^2\) as a reference point and review publications 10 years before and 10 years after it. This decision aimed to ensure higher current relevance of the publications analysed and explore the impact of the Strategy on programme theories.

This resulted in a main dataset of 2,832 citations.

2. **Initial screening of the main dataset – refinement of inclusion-exclusion criteria; levels of relevance and saturation**

Relevance of a piece of evidence in the realist approach is determined relative to the programme theory being tested and refined. As the theory itself is under development – from the initial “rough” programme theory to the more refined realist programme theory which should be the outcome of the review – relevance is a dynamic and, at least initially, underspecified concept.

Inclusion and exclusion criteria thus cannot be decisively fixed during early stages of the review process or, if done, the explanatory potential of the review may be constrained. In the case of diverse and complex interventions, as was our case of programmes for palliative and end of life care in primary care and the community, the specification of definitive inclusion and exclusion is even more problematic.

Consequently, while we were guided by the set of inclusion-exclusion criteria outlined in the PROSPERO protocol (summarised in Box 1 below) and the rough programme theory developed within the team and consulted with stakeholders (Appendix 2), we still worked within relatively flexible boundaries of relevance, capable of accommodating the realist approach in the context of a highly complex topic.

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Box 1: Summary of inclusion-exclusion criteria as per PROSPERO protocol
https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=97218

**Age:** “Adults (over 18 years of age) whose death is perceived as imminent or who have advanced, progressive or incurable conditions. As realist reviews focus on theory development, we may, where relevant, consult literature on other populations, e.g. paediatric patients.”

**Interventions/ exposures:** “Programmes, interventions, initiatives, approaches, tools, etc. for the provision of palliative and end of life care in primary care and other community settings.”

Definition of end of life care referred to the last 12 months of life. Definition of palliative care (WHO) referred to physical, psychosocial and spiritual suffering. See details in full protocol.

Understanding of primary care and the community: mostly in opposition to hospital care and hospice inpatient care.

Examples of programmes of interest:
- the upskilling of General Practitioners and the support for optimising provision of palliative and end of life care in general practice (i.e. primary care-based programmes);
- care provided by palliative care specialists in the patients’ homes or as hospice outpatient services;
- initiatives aimed at improving end of life care in care homes;
- programmes which are developed, funded and staffed fully or primarily by charities and the voluntary sector;
- programmes offered by the private sector, e.g. paid-for care in patients’ homes;
- virtual community initiatives.

**Main outcomes:** 1) “good death”, typically as experienced by the family and carers of the deceased; 2) quality of care, as experienced by the patient, their family and carers, and healthcare staff, or as measured by quantitative metrics; 3) cost effectiveness.

**Additional outcomes:** coordination of care; reduction of unnecessary and unwanted hospital admissions; place of death.

**Study design:** No restrictions on study design. Non-empirical work also included.

Citations were first screened at the level of title, abstract and keywords by MP. The protocol envisaged that a second reviewer would screen 20% of all citations. Double screening in the context of systematic reviews with a strong interpretative component is typically seen as a way of enriching the analysis as opposed to enabling the checking for and correction of errors. In this review, we considered it a way of enhancing the process of theory development. As the team member who had started the double screening process left the institution, this work was not completed. Relative to the numerous other corrective and enriching processes established for the study (study team meetings; meetings of researchers conducting realist reviews across the Evidence Synthesis Working
Group; meetings with a professionals’ Advisory Group and a Patient and Public Involvement Group; individual consultations with GW, the methodological expert on the study, etc.) and the openness to interpretative differences of any conceptual/theoretical review, we decided not to make alternative arrangements for double screening.

As opposed to aiming for a binary include-exclude decision, the process of screening was one of annotating citations for level of perceived relevance. Often, a brief note was added to the EndNote record to explain the decision, especially if it was not immediately clear from the paper title.

Inclusion categories:
- **Include, (potentially) core contents** – these citations were perceived as matching fully, or very closely, the questions of interest. In the majority of cases, they also fitted fully the main inclusion criteria (palliative and end of life care, community, UK, adults).
- **Include** – the generic ‘include’ category.
- **Include, broad** – for citations that covered topics outside of palliative and end of life care, community settings, adults and/or the UK, but suggested arguments and evidence that were relevant to the rough programme theory and its testing and refinement. Typically, the deviation from exemplary relevance was on 1 or 2 of the main inclusion criteria. If it was on more, the paper was more likely to be annotated as ‘maybe include’ (see below). That said, no numerical rule was followed around degrees of relevance.

Exclusion categories:
- **Exclude** – the generic ‘exclude’ category. The majority of directly excluded papers were from the basic sciences and from developing world healthcare systems (whose context we have pre-judged as too different to be sufficiently relevant).
- **Exclude, search precision-relevant** – we noticed that a number of terms (such as “C-terminal”, “N-terminal”, “carboxyl-terminal”, “terminal half-life”) reappeared frequently and consistently picked false positives, while never picking true positives. We started annotating such papers as an opportunity to explore strategies for improving the specificity of subsequent searches.
- **Exclude, unrecognised duplicate** – despite having conducted an automatic de-duplication of the dataset, duplicates were still appearing.
Exclude, yet broad relevance – such papers had some relevance to issues of interest, but those issues were typically too broad features of the topic (e.g. overall tendencies in the distribution of staff across the health workforce).

Exclude, but preserve for bereavement review – those papers addressed bereavement in primary care and the community, with the team commencing a realist review on complicated grief around the time of the screening. Under different circumstances, papers from this category would have been distributed across ‘exclude’ and ‘include’ categories. A small number of bereavement papers were included in this review too, but only to the extent to which they illuminated care before death.

Uncertain categories

Maybe – these were papers which 1) concerned settings, populations and geographies that fell under our exclusion criteria (e.g. hospital, children, non-UK), but some of the CMO configurations or elements they pointed towards appeared transferable; 2) had title/abstract/keywords which were not clear enough for a definitive decision; 3) discussed core ideas within the field of palliative and end of life care which could help elicit fundamental, but potentially too generic, CMO-configurations (as in papers on the history of palliative care); 4) explored highly specific settings and contexts of death and dying (e.g. prisons, suicides) which we were not excluding, but were not expecting to cover in detail either.

Include on limited information – the title, abstract, and keywords suggested ‘include’, but there was a significant level of uncertainty to the decision due to limited information.

Exclude on limited information – the title, abstract, and keywords did not give sufficient justification to follow up a paper to its full text, but there was a significant level of uncertainty to the decision due to limited information.

After screening 1,226 citations out of the main dataset (of 2,832), a level of saturation was achieved. Reaching saturation at this stage – roughly half of the dataset – was also taken as an opportunity to use half of the dataset for theory development (over and above that of the rough programme theory) and the other half for theory testing. The table below presents the proportions of the different levels of relevance of citations.
### LEVEL OF RELEVANCE

<table>
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<th>% of 1226 total</th>
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### 3. Targeted searches

Targeted searches – both simple and refined (the latter developed by IK, the library and information specialist on the project) – were run at various stages in the process of narrowing the review focus.

Main topics included:

- 24/7 specialist palliative care services
- night sitting, night nursing, care at night
- rapid response services
- referrals in palliative and end of life care
- staff shortages (in the NHS generally and palliative care more specifically), with implications for time available for patient care
- impact of performance management approaches (measurements, targets, incentives, etc.) on the work done (how “time is invested”)
- family size, structure and dynamics, and health of carers
- systematic reviews on prognosis in palliative and end of life care and/or predictions of survival or death.

Apart from the last topic (search strategy given at the end), all other topics were gradually excluded from the review focus. However, a number of the papers included in the review were found through those supplementary searches.
Main search, version 3

End of life AND Primary Care AND Britain

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1990 onwards

Searches run 24th April 2018

Medline

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid

MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

exp terminal care/ or exp palliative care/ or exp palliative medicine/ or exp terminally ill/ or exp hospices/ or ((end adj of adj life) or palliative* or terminal* or hospice*).ti,ab. or (last adj1 (week* or month* or day*)).ti,ab.

AND

(exp primary health care/ or exp community health services/ or exp home care services/ or exp general practice/ or exp family practice/ or exp charities/ or exp volunteers/ or exp organizations non-profit/ or exp community health nursing/ or exp spouses/ or exp home nursing/ or exp home care services/ or exp homes for the aged/) or

((Lay adj (care* or work*)) or volunteer* or (third adj sector) or (non-profit* or nonprofit*) or charit*
 or spouse* or wife* or wives* or husband* or partner* or (home* adj2 (care or residential* or
 nursing* or (old adj (folk* or person* or people*)))) or (primary adj (care or healthcare or (health adj
care))) or (general adj practi*) or (family adj (practi* or doctor* or physician*)) or (community adj2
(care* or healthcare or nurs* or (old adj (folk* or person* or people*)))) or (district* adj nurs*) or (marie adj curie) or
(macmillan adj2 (nurs* or service* or support*)))).ti,ab.

And

(exp united kingdom/ or (national health service* or nhs).ti,ab,in. or (gb or "g.b." or Britain* or
(british* not "british Columbia") or uk or "u.k." or united kingdom* or (england not "new england")
or northern ireland* or northern irish* or scotland* or Scottish* or ((wales or "south wales") not
"new south wales") or welsh).ti,ab,jw,in.)


And

(theor* or model* or concept* or philosoph* or program*).mp.

Embase

Embase 1974 to 2018 April 02

exp *terminal care/ or exp *palliative therapy/ or exp *terminally ill patient/ or exp *hospice/ or
((end adj of adj life) or palliative* or terminal* or hospice*).ti,ab. or (last adj1 (week* or month* or
day*)).ti,ab.

AND

(exp *primary medical care/ or exp *community care/ or exp *home care/ or exp *general practice/
or exp social welfare/ or exp non profit organization/ or exp volunteer/ or exp community health
nursing/ or exp spouse/ or exp home care/ or exp nursing home/ or exp home for the aged/)

Or

((Lay adj (care* or work*)) or volunteer* or (third adj sector) or (non-profit* or nonprofit*) or charit*
 or spouse* or wife* or wives* or husband* or partner* or (home* adj2 (care or residential* or
 nursing* or (old adj (folk* or person* or people*)))) or (primary adj (care or healthcare or (health adj
care))) or (general adj practi*) or (family adj (practi* or doctor* or physician*)) or (community adj2
(nurs* or service* or support*)).ti,ab.)
(care* or healthcare or nurs* or compassionat*)) or (district* adj nurs*) or (marie adj curie) or (macmillan adj3 (nurs* or service* or support*))).ti,ab.

And

(exp *united kingdom/ or (national health service* or nhs).ti,ab.in. or (gb or "g.b." or Britain* or (british* not "british Columbia") or uk or "u.k." or united kingdom* or (england not "new england") or northern ireland* or northern irish* or scotland* or Scottish* or ((wales or "south wales") not "new south wales") or welsh).ti,ab,jx,in.)

And

(theor* or model* or concept* or philosoph* or program*).mp.

Web of Science

TOPIC: (thelor* or model* or concept* or philosoph* or program*)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC
Timespan=All years

TOPIC: (united kingdom or uk or gb or great britain or england or scotland or northern ireland or wales or welsh or scottish or northern irish or great britain or great british or nhs or "national health service")
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC
Timespan=All years

TOPIC: (((Lay adj (care* or work*)) or volunteer* or (third near/1 sector) or (non-profit* or nonprofit*) or charit* or spouse* or wife* or wives* or husband* or partner* or (home* near/2 (care or residential* or nursing* or (old near/1 (folk* or person* or people*)))) or (primary near/1 (care or healthcare or (health near/1 care))) or (general near/1 practi*) or (family near/1 (practi* or doctor* or physician*)) or (community near/2 (care* or healthcare or nurs* or compassionat*)) or (district* near/1 nurs*) or (marie near/1 curie) or (macmillan near/3 (nurs* or service* or support*))))
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC
Timespan=All years

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SCIE Social Care Online

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nurse or marie curie or macmillan or charity or charities or volunteer or voluntary or nursing home
or care home or home for the aged or residential care

and

theory or model or programme or program or concept or philosophy

Targeted search on systematic reviews on prognosis in palliative and end of life care and/or
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Appendix 5: Further detail on programme types

Box 3, complete version: Types of palliative and end of life care programmes in primary care and the community in terms of broad programme logic expressed as CMO-configurations

Note: Here we offer a typology of palliative and end of life care programmes in primary care and the community in terms of the overarching, generic theory (taking the form of a CMO-configuration) to which they appear to subscribe. We have abstracted the high-level, generic CMOs from specific CMOs characterising the example programmes analysed, with the examples coming from the 253 “core contents” citations.

For instance, on the basis of the brief programme descriptions we have reviewed, we suggest that the abstract mechanism underpinning innovative discharge roles is the management of boundaries between services and settings. Similarly, we suggest that intermediate care beds can be thought of as a boundary management initiative – both between service types (hospital and community) and patient needs (requiring intense professional input and oversight – requiring more limited professional input and oversight). Thus, two programmes which may “look” very different belong, in our classification, to the same type by virtue of their shared theoretical underpinning – shared programme logic of mechanisms causing their outcomes. Much further work is required to elicit the theories behind the specific programmes included here and to test our choices of a “defining theory”.

Appendix 5 to Petrova, Wong, Kuhn, Wellwood & Barclay, “Dying and Time”, Mar 2021
Type 1 programmes: Programmes seeking to improve the availability of services where systemic and critical gaps exist: in terms of time, location, intensity and responsiveness (when, where, how much and how quick)

When palliative care is needed in time periods outside of normal working hours and in underserved areas (C), end of life care outcomes will improve dramatically and efficiently (O) only if services are time-of-the-day-independent (M), adapted to the location where they are offered (M), flexible (M) and responsive (M).

Examples of Type 1 programmes that address time and timing

24/7 services
Out of hours (OOH) services
- OOH specialist palliative and end of life care services
- OOH pharmacy provision of drugs
- OOH generalist services
- “Informal” OOH services (e.g. GP providing personal phone number)
- “Twilight” services (in the underserved periods between daytime and OOH services)

Night services
- Night nursing
- Night sitting

Hospice day care services

Rapid response services

Examples of Type 1 programmes that address location, coverage and proximity

Home-based services, including Hospice at Home

Hospice outpatient services

GP practice palliative and end of life care clinics

Community centres services

Host family respite

Rural services

Telecare services

Deprived areas services

(relative) Services moving closer to the users

Examples of Type 1 programmes that address intensity and responsiveness

Rapid response services

Improved standard practice (new types of prioritisation)

Type 2 programmes: Programmes defined through the broad aspect of our humanity and needs being addressed, often as forms of care and support provided by a particular professional or lay group

As suffering and pain are multimodal (C), we can achieve better quality of life for dying patients (O) when we acknowledge the numerous modalities of experiencing pain and suffering and by acting in (more) holistic ways (M).

Subtypes of Type 2 programmes in terms of the form of therapy or support offered

Alternative and complementary therapies

Arts and art therapy

Basic body comfort
- Hands-on enablement
- Equipment-enabled comfort

Basic human presence and support – being with, staying with; bridging the “dying world” and the “world outside”; small, intangible acts of kindness

Beauty and wellness

Clinical and medical care

Financial support and advice

Hands-on care

Holistic care

Movement, exercise, physiotherapy

Nature, gardens, the outdoors

Personal care support

Psychological support and counselling

Rehabilitation

Respite
- Day care respite
- Host family respite
- In-home respite
- Institutional respite
- Video respite

Social support
- Opportunities for meeting people
- Social activities
- Social environment as created by volunteers
- Social support from fellow patients
Type 3 programmes: Programmes addressing the management of boundaries and transitions

As the needs of dying patients at transition points can be extra complex (C) and different services often lack sufficient levels of integration and coordination (C), we can enable each patient to receive the most appropriate and timely care within resource limits (O) if we manage service boundaries and transitions better, in rational yet person-centred ways (M).

Examples of Type 3 programmes that address discharge management
- Rapid hospital discharge to enable home death
- Discharge roles (e.g. Discharge Community Link Nurses)
- Discharge letters and templates
- Discharge policies and pathways
- Discharge practices when palliative care needs reduced or prognosis modified

Examples of Type 3 programmes that address referral management
- Clarification of referral criteria (triggers) and development of documentation
- Rules on referral initiators – who can refer?
- Rules on referral timing – when to refer?
- Referral triggers – what needs to happen so as to refer?
- Referral audits for quality improvement

Examples of Type 3 programmes that address “midway solutions” between service types
- Intermediate care beds
- Community hospitals
- Hospice at Home services
- Primary care doctors with visiting rights to local hospitals

Examples of Type 3 programmes that address the management of transitions and working across settings
- “Alignment models”, e.g. aligning the work of GPs and care homes
- Bridging roles – liaison roles, secondments, dual roles
- Case reviews across settings
- Electronic data sharing, Electronic Palliative Care Coordination Systems (EPaCCS)
- Hand-over protocols and forms, particularly for OOH
- Multidisciplinary team meetings
- Service integration work
- Transportation across settings
- Partnerships between ambulance service and other settings

Type 4 programmes: Programmes prioritising patient-centredness, ownership and empowerment

As patients and their carers have a range of diverging end of life care needs, preferences and wishes (C), we are far more likely to achieve the goals of care that truly matter to them (O) if these are clearly elicited, recorded and acted upon (M) and, more broadly, if services are co-developed with patients and carers (M).

Subtypes of Type 4 programmes with examples

Programmes centred around tools for eliciting and recording patient preferences and wishes for end of life care
- Preferences elicitation and care planning tools – e.g. Preferred Priorities of Care, EPaCCS, ReSPECT
- Legally binding tools – e.g. Advanced Directives to Refuse Treatment (ADRT)
- Design of new tools
- Training and support for the use of existing tools
- Broader initiatives for increasing the uptake of such tools

Programmes based on shared decision-making innovations
- Patient-led case conferences

Programmes based on support for self-management

Programmes for co-developing services with patients
- Peer education programmes for older people about Advance Care Planning

Programmes for community-based discussions of end of life care
**Type 5 programmes: Programmes addressing different phases of an illness or of the dying process**

As the phase in the trajectory of an illness and/or the proximity to death of a patient has a profound impact on their treatments and care needs, we can improve outcomes for patients and support the sustainability of the health service by structuring and delivering services in a phase-centric way which enables their optimisation, with no relevant needs missed and no unnecessary activities undertaken.

**Subtypes of Type 5 programmes (perhaps more often presenting as service structures and pathways than new programmes)**

- Services around the delivery of a terminal diagnosis
- Services during active treatment
- Services after discharge
- Services at recurrence/exacerbation
- Services in the final weeks and days of life
- Anticipatory bereavement
- Bereavement support

**Type 6 programmes: Programmes taking a systemic approach**

As the terminal phase of an illness or the process of dying can be very complex and fast changing and involve a large number of services, we are more likely to achieve positive outcomes for the patients, their family and the system if terminal illness and/or the process of dying is approached in a systematic, proactive and anticipatory manner rather than a piecemeal and reactive one.

**Subtypes of Type 6 programmes with examples**

- Programmes aiming to improve identification of patients in need of palliative and/or end of life care
  - Development of new prediction and risk stratification tools
  - Improving staff abilities in identifying patients at the end of life
  - Improving the skills of junior and lower level staff in communicating concerns about patients higher up the hierarchy
  - Appropriate recording and communication of such information to other services, e.g. through Registers (EPaCCS)
- Programmes enabling discussions of death, dying and care at the end of life
- Programmes aiming to improve Advance Care Planning (ACP)
  - Enhancing basic staff skills in using them
  - More in-depth training on using ACP tools, acknowledging challenges such as differences between family and patient preferences, dynamics of preferences, service limitations, creating the right environment for the conversations, etc.
  - Initiatives to support the broader, more systematic use of such tools
- Programmes aiming to improve integration of care and handling diffusions of responsibility
  - Case management initiatives
  - Key worker initiatives
  - Data sharing for improved informational continuity
  - Palliative care coordination centres
  - Bridging roles
- Programmes aiming to develop or refine existing protocols and pathways
- Programmes based on the use of decision-making tools
- Programmes aiming to improve monitoring and evaluation systems and processes
  - Enhanced annual reviews of patients
  - Patient recall systems and processes
  - Palliative and end of life care registers and dashboards
  - Provision of (comparative) data on palliative and end of life care processes and outcomes
- Programmes facilitating internal change through external support
  - Peer facilitation for practices
  - Educational facilitation
- Programmes creating a broad supportive environment
  - Financial incentives
  - National guidance
  - Local change management initiatives
  - Identifying and supporting ‘champions’
- “Meta-programmes” – highly systematic ways of developing new local initiatives and programmes

Appendix 5 to Petrova, Wong, Kuhn, Wellwood & Barclay, “Dying and Time”, Mar 2021
### Type 7 programmes: Programmes seeking improvements through staff and volunteer development

When work environments value palliative and end of life care training and development as part of their business-as-usual rather than a matter of short-term projects (C), palliative and end of life care provision across the board improves (O) through investment in the knowledge, skills, motivation, attitudes, etc. of professionals and lay persons providing care (M) and through creating effective role structures and arrangements (M).

#### Subtypes of programmes and examples

**Programmes based on developing new staff roles and forms of task distribution**
- Extended nurse prescribing in palliative care
- Peer facilitators with ‘dual roles’ (e.g. GPs with special interest in PEoLC)
- Bridging roles

**Programmes for staff training and support**
- From palliative care specialists to generalist staff
- Training in specific skills
  - Communication
  - Palliative and end of life care prescribing
  - Advance Care Planning
  - etc.
- Training for specific staff groups
- Training by using different approaches, contexts and platforms (hands-on, online, on-the-job, etc.)
- Support for generalist staff, or even specialist staff, in dealing with rare diseases

**Programmes expanding the roles of volunteers and community members**
- Compassionate cities initiatives
- Volunteers in hospices
- Death dealers

### Type 8 programmes?: Programmes defined through the support they provide to informal carers?

The presence of carer-focused programmes in the research literature, as sampled, was not on a par with the presence of programmes of the other seven types. Further research is needed on the degree to which support for informal carers in palliative and end of life care translates into programmes which are defined in terms of their carer-focused mechanisms rather than including them as a secondary component.

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*Appendix 5 to Petrova, Wong, Kuhn, Wellwood & Barclay, “Dying and Time”, Mar 2021*
Appendix 6: CMO-configurations and supporting evidence on the identification of patients at the end of life, short-term prognosis and associated referrals

The Appendix has 3 parts:

- Excerpts from UK policy documents and reports concerning the identification of end of life care (EoLC) patients
- Supplementary Table 1: Context-Mechanism-Outcome configurations around identification, prognosis and referrals based on them
- Supplementary Table 2: Abstract-level scoping of most recent (last 5 years) systematic reviews on prognosis

1. Excerpts from UK policy documents and reports concerning the identification of end of life care (EoLC) patients

The list of excerpts is illustrative. The documents chosen were considered as highly likely to have had significant impact on palliative and end of life care services and practice in England, by virtue of being prepared by broad coalitions of UK palliative and end of life care organisations; the UK Government/Department of Health and Social Care; the UK Parliament; and NICE, the National Institute for Health and Care Excellence (a non-departmental public body of the UK Department of Health and Social Care), which provides national guidance and advice to improve health and social care).

Even if far from exhaustive, we believe the list gives a sufficiently reliable overview of the mainstream position around patient identification in current UK palliative and end of life care policy and practice. We have also made sure to include caveat statements (around the challenges of identification and uncertainty at the end of life), even if they are not too prominent in a document. They are indicated by (uncertainty) preceding a statement. Our arguments criticising the mainstream view concern the lack of sufficient recognition of the challenges of prognosis and identification rather than a complete lack of it. However, this lack of balance, we claim, leads to a range of important unintended negative consequences.

The documents are arranged in chronological order. Statements are direct quotes (indicated by italics; or if the document quotes a contributor, by italics and inverted commas, with the source added). Minimal connecting or clarifying statements have been added by us (normal font).

Q followed by a number (e.g. Q7) is a unique identifier for quotes referred to in the table of Context-Mechanism-Outcome configurations further below.

1 https://en.wikipedia.org/wiki/National_Institute_for_Health_and_Care_Excellence
2 https://www.nice.org.uk/about
Q 1. The [EoLC] care pathway involves the following steps:
   - Identification of people approaching the end of life and initiating discussions about preferences for end of life care;

   [6 further steps follow] (p. 9-10)

Q 2. Many health and social care staff have had insufficient training in identifying those who are approaching the end of life, in communicating with them or in delivering optimal care. To address this, a major workforce development initiative is now needed, with particular emphasis on staff for whom end of life care is only one aspect of their work. (p. 12)

Q 3. (uncertainty) The definition of the beginning of end of life care is variable according to individual person and professional perspectives. (p. 47)

Q 4. The major challenges in relation to the delivery of high quality end of life care in the community include:
   - Poor identification, assessment and coordination of end of life care within some general practices;

   [6 further challenges follow] (p. 84)

Q 5. (uncertainty) It is difficult, if not impossible, to calculate the cost of end of life care in this country. This is partly because of the difficulty in defining exactly when end of life care starts. (p. 150)

1 Department of Health. End of Life Care Strategy (Jul 2008).
House of Commons Health Committee report (Mar 2015)

Q 6. The situation is unlikely to improve unless clinicians feel confident to identify people who may be near the end of life and to start conversations with their patients about their wishes. (p. 3, Summary)

Q 7. “The NHS continues to struggle to properly identify people who are in the last stages of life, unless they have a terminal or otherwise life-threatening condition ... This in turn means people are not able to plan properly or encouraged to discuss decisions about their future care ... A failure to understand multi-morbidity and frailty and the trajectory of people’s health living with either (or often both) means the NHS is not agile, failing to allow care and support to switch tracks quickly when someone is approaching the end of life.” (from Age UK written evidence to inquiry; p. 14)

Q 8. The Sue Ryder Care Centre for the Study of Supportive, Palliative and End of Life Care has also found that staff caring for frail and seriously ill older people have difficulty recognising the point at which a transition to a palliative care approach may be appropriate. (p. 14-15)

Q 9. Many of those who provided written evidence to this inquiry expressed the opinion that health care staff need support to develop their competence in identifying, providing care to and communicating with people at the end of life and their families and carers. (p. 20)

Q 10. “Our case work has shown that there is a need to communicate in a way that is both sensitive but also makes clear the prognosis and what options there are for care based on the outcomes individuals may want for themselves.” (evidence provided by the Parliamentary and Health Service Ombudsman; p. 20)

Q 11. “When patients are not informed about their prognosis and are not asked about their care and medical treatment preferences, they are denied the right to participate in decisions and might not have the death they want.” (evidence provided by Compassion in Dying; p. 21)

Q 12. Witnesses to the inquiry expressed concern that there is a lack of research evidence to inform the development of models for early identification of those people who would benefit from receiving palliative care and how to deliver palliative and end of life care services to non-cancer patients. (p. 39)

---

Q 13. (uncertainty acknowledged; then largely overridden) We know that much about recognising dying and impending death is uncertain and challenging. However, timely identification and honesty where there is uncertainty is key to the quality of care – all else follows. (p. 18)

Q 14. Effective systems for person centred care need to encompass: systematic ways of reaching people who are approaching the end of life, effective assessment as well as effective decision making support, care coordination, care planning, and care delivery. (p. 19)

Department of Health. The Government Response to the Review of Choice in End of Life Care (Jul 2016)\(^6\)

Q 15. Good care is also about identifying people approaching the end of life earlier so that there is time and opportunity to prepare, discuss and plan care, and time to put that care in place to meet people’s individual needs and preferences. (p. 19)

Q 16. (uncertainty) The AMBER care bundle is a simple approach used in hospitals when there is clinical uncertainty of recovery. The approach supports staff, patients and families who wish to continue with treatment in the hope of a recovery, while encouraging open conversation about people’s wishes and preferences should things get worse rather than better. (p. 21)

Q 17. All CCGs should also be clear about the efficiency gains to be made when people are able to make plans and express preferences early about their care so that unnecessary hospital admissions are avoided. We know that people’s experiences of care are better and services more coordinated and efficient when clinical staff can identify people’s needs earlier and share and implement end of life care plans more easily. (p. 25-26)

\(^5\) National Palliative and End of Life Care Partnership. Ambitions for Palliative and End of Life Care: A national framework for local action 2015-2020 (Sep 2015).

National Institute for Health and Care Excellence guideline for service delivery (Oct 2019)\(^7\)

**Q 18.** (uncertainty) *End of life care includes the care and support given in the final weeks and months of life, and the planning and preparation for this. For some conditions, this could be months or years.* (p. 35)

**Q 19.** First recommendation in Guideline is about: 1.1 *Identifying adults who may be approaching the end of their life, their carers and other people important to them.* (p. 7)

**Q 20.** *People managing and delivering services should develop systems to identify adults who are likely to be approaching the end of their life (for example, using tools such as the Gold Standards Framework, the Amber Care Bundle or the Supportive and Palliative Care Indicators Tool [SPICT]). This will enable health and social care practitioners to start discussions about advance care planning, provide the care needed, and to support people's preferences for where they would like to be cared for and die.* (p. 7)

**Q 21.** (uncertainty acknowledged; then largely overridden) *Although the evidence was limited, the committee agreed that identifying adults who may be approaching the end of their life supports health and social care practitioners to start discussions about advance care planning. This should ensure that the person near the end of life is provided with the support that they may need now or later to help them stay where they would like to be cared for and die. It also gives them time to consider and re-evaluate their needs with their health and social care practitioners.* (p. 22)

**Q 22.** *The committee wanted to emphasise the importance of identifying people systematically. There are already some systems in use for identifying people approaching the end of their life, which are given as examples in the recommendations. However, there were no studies comparing and evaluating their effectiveness in service delivery so the committee could not recommend a particular system.* (p. 22)

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### 2. Supplementary Table 1: Context-Mechanism-Outcome configurations around identification, prognosis and referrals based on them

The row below is illustrative to help explain the structure of the table and the abbreviations and symbols used in it, presented in the notes that follow.

<table>
<thead>
<tr>
<th>Parameter type and identifier</th>
<th>Context-Mechanism-Outcome (CMO) configurations or elements</th>
<th>Sources</th>
<th>Key pieces of evidence, theoretical claims and interpretations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Timely identification of end of life stage as enabling preparation</td>
<td>Sims-Gould et al. 2010 quoting Steinhauser et al. (trigger)</td>
<td>(A, M, O) Identification enables preparation which, in turn, enables meeting an individual's needs and preferences and achieving a good death</td>
</tr>
<tr>
<td>A, C, M, O</td>
<td>The identification of patients who are likely to be in the last year of their lives (A/O \text{intermediate}) allows sufficient time for discussing, planning, organising and coordinating care around a patient's needs, wishes and preferences (M), for instance around their preferred place of care (O); their family's needs and capacity (M/C); the availability of local services (C); and in view of the sustainability of the health system (C).</td>
<td>Core policy documents (see pp. 2-5 above)</td>
<td>Programme theory 'seed' statements</td>
</tr>
<tr>
<td>Original programme theory</td>
<td>In terms of broader life (C), such identification allows ... [continues below]</td>
<td>Roikjær et al. 2019 *** BROADER (hospital)</td>
<td>Department of Health, 2016. The Government Response to the Review of Choice in End of Life Care</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Domain knowledge of team</td>
<td>“Good care is also about identifying people approaching the end of life earlier so that there is time and opportunity to prepare, discuss and plan care, and time to put that care in place to meet people's individual needs and preferences.” (p. 19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>National Institute for Health and Care Excellence guideline for service delivery, 2019</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>“People managing and delivering services should develop systems to identify adults who are likely to be approaching the end of their life ... [continues below]</td>
</tr>
</tbody>
</table>
Context-Mechanism-Outcome (CMO) configurations or elements

The CMOs presented in the table can be complete configurations, partial ones (e.g. M-O, C-O) or, occasionally, individual elements (C, M, O). If only the latter, they have been included because they appear to have significant explanatory potential, but either cannot be weaved in a complete CMOs yet or can contribute to many (typically the C-element). At times, A, for programme activity, is also added to make the explanations clearer and better connected to ‘visible’ features of a programme. Longer CMO-configurations are introduced by a brief heading, which can be based on any of the elements.

CMO colour coding

**Green** CMOs or elements are the ones intended and (partly) articulated by the original programme theory. The versions offered in the table are refinements of the rough programme theory.

**Black** indicates that particular negative CMO configurations are recognised by the original programme theory. In fact, the latter is often developed as an attempt to address them.

**Red** indicates CMO configurations which are not, or only minimally, recognised by the original programme theory but limit its applicability. In such configurations, M is a countervailing mechanism, C is a context blocking the functioning of the programme theory mechanisms, and O is a resulting outcome.

**Yellow** is for CMO configurations or elements which are consistent with the original programme theory but are mentioned only minimally and remain mostly tacit.

**Abbreviations**

The following are non-standard conceptual subtypes and notations (non-standard in the realist method) we have been experimenting with for additional accuracy of attributions:

- A – programme activity
- A fail – used to indicate a failure to perform a programme activity
- O multiple – sets of outcomes which tend to co-occur
- O intermediate – indicates outcomes that are elements of a chain of steps and dependencies which may lead to primary outcomes. Primary outcomes may be patient-relevant, carer-relevant, health professionals-relevant and health system-relevant.
M/O, C/M or other combinations – when an element can perform more than one formal function, depending on the perspective.

**Symbols differentiating reference types (sources column)**

**Asterisks** indicate a process of literature searching and identification other than the core search (no asterisk means the reference is from the core search):

- * indicates references from a focused, targeted search – searches conducted with the goal of further specifying and testing the theories under development (search strategies in the Literature searching appendix);
- ** indicates references obtained through citation tracking – following up on work referenced in the papers we have been analysing or using forward citation tracking (looking up papers which cite the one being reviewed);
- *** indicates a reference from the pre-existing collections of the authors, recommendations from colleagues or serendipitously identified papers.

**BROADER** indicates that the source did not fall fully within the scope of the review in terms of its theme (palliative and end of life care), geography (England, potentially UK) and population (adults). Using such broader resources is entirely in line with the realist approach and, in fact, an expression of its exploratory logic. The particular “deviation” from an exemplary source is shown in brackets:

- BROADER (country – e.g. Australia)
- BROADER (domain – e.g. mental health)
- BROADER (population – e.g. children).

**Sims-Gould et al. 2010 (trigger)** – i.e. smaller font sources followed by “(trigger)” were the first sources to prompt us to code an issue, but the latter was a relatively marginal point in them. Typically, we have sought further sources to refine the CMO-configurations of interest and to substantiate them with evidence/ theoretical claims.

The realist approach relies heavily on the so called “nuggets of evidence”. One way to describe them is as minor, peripheral claims or data in a source document, which, however, provide a pertinent confirmation/ refutation of a hypothesis from the realist study. The awareness of the value of nuggets of evidence meant that, especially early on, we have been coding minor mentions of issues because of their relevance rather than richness and depth.
Furthermore, most primary care and community interventions in palliative and end of life care are complex interventions, meaning they have many elements, many of which do not receive focused attention in a publication.

Finally, publications in any research field have a sufficiently shared discourse and background. Core ideas emerge quickly from any set of publications. Which came first is a matter of the approach to literature searching and the chronology of analysis. Also, any researcher familiar with the domain (and we are) can formulate a broad range of statements from its discourse provided a trigger.

Such sources are included for transparency and to support explorations of the potential impact on the review outcomes of the literature searching approach and chronology of reading/coding.

**Domain knowledge of team** – occasionally, this has been added to the source column. Some CMO-configurations were refined or expanded through the background knowledge of the domain experts on the team (SB and MP for PEOlc and SB and GW for general practice). If a statement appears in the CMO-configuration without a corresponding evidence in the last column, then it was based on such broader domain knowledge. This has only been done for claims we consider uncontroversial, “givens” in the field of (UK) palliative and end of life care, and which, precisely because of being taken for granted by insiders, are not always made explicit.

**Key pieces of evidence, theoretical claims and interpretations**

If the evidence, theoretical claims and interpretations in the last column are coming from an empirical study and from its own data (rather than its background literature review, for instance), we have included a brief description of its (Setting/Participants) and (Methods) to help readers evaluate the credibility of the evidence and its relevance to their own work. If the authors’ description is not transparent enough of important study limitations, we add further critical comments and caveats to the brief Methods description. These setting/participants and methods overviews have been developed in a holistic way, e.g. without the use of a systematic checklist to assess or include parameters.
When the supporting statements added to this column are not empirical evidence or if, while based on evidence, make a significant leap from it (as in the discussion section of a paper, for instance), we have added an indication:

- Programme theory ‘seed’ statements – for excerpts from policy documents or reports we have used as a ‘seed’ to grow a rough programme theory. They are relevant evidence in the sense of serving to demonstrate the validity of our rough programme theory. They are often based on some evidence, but this is rarely made explicit in the statement.
- Explanation for pattern of data – typically offered by the authors of a paper. It is based on evidence but makes a theoretical leap from it.
- Framing sections evidence/ statement – evidence or statements which come from the background (introduction) or discussion of a paper. As they are presented briefly, they often lack detail and indications of the trustworthiness of the original source.
<table>
<thead>
<tr>
<th>Parameter type and identifier</th>
<th>Context-Mechanism-Outcome (CMO) configurations or elements</th>
<th>Sources</th>
<th>Key pieces of evidence, theoretical claims and interpretations</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROGNOSIS, TIMELY IDENTIFICATION</td>
<td><strong>1.1. A, C, M, O Original programme theory</strong>&lt;br&gt;Timely identification of end of life stage as enabling preparation&lt;br&gt;The identification of patients who are likely to be in the last year of their lives (A/O &lt;i&gt;intermediate&lt;/i&gt;) allows sufficient time for discussing, planning, organising and coordinating care around a patient’s needs, wishes and preferences (M), for instance around their preferred place of care (O); their family’s needs and capacity (M/C); the availability of local services (C); and in view of the sustainability of the health system (C).&lt;br&gt;In broader life, outside of the contexts of healthcare (C), such identification allows both patients and carers to prepare for death and develop a level of acceptance of it (M/O), such as through putting their affairs in order (M/O), making the best of the time they have got left (M/O), completing what has been left undone or finding better closure for it (M/O), settling and healing relationships (M/O), expressing love, regret, forgiveness, gratitude, appreciation ... (M),</td>
<td>Sims-Gould et al. 2010 quoting Steinhauser et al. (trigger)&lt;br&gt;Core policy documents (see pages 2-5 above)&lt;br&gt;Roikjaer et al. 2019 *** BROADER (hospital)&lt;br&gt;Domain knowledge of team</td>
<td>(A, M, O) Identification enables preparation which, in turn, enables meeting an individual’s needs and preferences and achieving a good death&lt;br&gt;Programme theory ‘seed’ statements&lt;br&gt;Department of Health, 2016. The Government Response to the Review of Choice in End of Life Care&lt;br&gt;“Good care is also about identifying people approaching the end of life earlier so that there is time and opportunity to prepare, discuss and plan care, and time to put that care in place to meet people’s individual needs and preferences.” (p. 19)&lt;br&gt;National Institute for Health and Care Excellence guideline for service delivery, 2019&lt;br&gt;“People managing and delivering services should develop systems to identify adults who are likely to be approaching the end of their life (for example, using tools such as the Gold Standards Framework, the Amber Care Bundle or the Supportive and Palliative Care Indicators Tool [SPICT]). This will enable health and social care practitioners to start discussions about advance care planning, provide the care needed, and to support people’s preferences for where they would like to be cared for and die.” (p. 7)</td>
</tr>
</tbody>
</table>
reminiscing about their life (M) and finding a sense of value and meaning in it (M/O), and leaving a legacy for future generations (M/O).

Identification of the end of life stage (A) is thus crucial for enabling the best possible outcomes for the patient, their family and other people important to them, and for the sustainability of the health system (e.g. by avoiding unnecessary admissions and interventions) (O multiple).

See also the policy quotes on pages 2-5, in particular Q7, Q11, Q17 and Q21.

(M, O) Having time to prepare for death and reflect on one’s life seen as aspects of a good death by patients and carers

Sims-Gould et al. 2010

“Steinhauser et al. (5) studied the perspectives of patients and their families on a good death and found that it would include: completion (adequate time to prepare for death); pain and symptom management; clear decision making; affirmation of the whole person; the opportunity to reflect on one’s own personal accomplishments and time to be with others.”

[M, O intermediate] Positive non-medical ways of preparing for death and positive experiences/outcomes that may result from them

Roikjær et al. 2019

“The interventions [using personal narratives in palliative care] were all relatively brief psychotherapy based on reminiscence theory in which patients re-evaluate past experiences with the intention of resolving and integrating past conflicts, bringing new significance and meaning to their life and empirical work on either dignity or end-of-life experience.44

“The framework underlying dignity therapy and legacy building was the model of dignity,45,46 which focuses on dignity-conserving tasks such as settling relationships, sharing words of love and preparing legacies of memory and shared values.”

“[The] outlook model has tasks very similar to the dignity model although they name them development tasks: sense of completion in

"
## 1.2. A, C, M, O

<table>
<thead>
<tr>
<th>Original programme theory</th>
<th>Functional equivalent of 1.1, negative framing</th>
<th>Mintzer and Zagrabbe 2007*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dangers of delayed identification of the end of life stage</strong></td>
<td><strong>(A, M, O)</strong> Lack of timely identification and/or communication of prognosis deprives patients of choice at the end of life and may lead to a bad death</td>
<td>BROADER (United States)</td>
</tr>
<tr>
<td><strong>Delayed identification of the end of life stage</strong> (intermediate)</td>
<td><strong>Programme theory ‘seed’ statement</strong></td>
<td>trigger</td>
</tr>
<tr>
<td>Patients may then feel robbed of time they believed they had (M/O), be denied the opportunity to have a choice in how they die (M/O), experience severe distress (O) and, ultimately, not have the death they wanted (O).</td>
<td><strong>House of Commons Health Committee report, 2015</strong></td>
<td></td>
</tr>
<tr>
<td>In the context of overburdened services (C) and lack of awareness of a patient’s preferences (M), health professionals may not make the best decisions (M), even when trying to do their best (M/C) and, for instance, undertake unnecessary interventions (M/O) or not be able to arrange the right services in time (M/O). This may result in suboptimal care; bad, even horrible, deaths; sense of guilt and frustration for the</td>
<td><strong>“When patients are not informed about their prognosis and are not asked about their care and medical treatment preferences, they are denied the right to participate in decisions and might not have the death they want.”</strong> (p. 21; evidence provided by Compassion in Dying)</td>
<td></td>
</tr>
</tbody>
</table>

### Mintzer and Zagrabbe 2007*

* Denotes Trigger

**A, C, M, O** Lack of timely identification and/or communication of prognosis deprives patients of choice at the end of life and may lead to a bad death

**Programme theory ‘seed’ statement**

**House of Commons Health Committee report, 2015**

“...” (p. 21; evidence provided by Compassion in Dying)

**A, C, M, O** Lack of timely identification and/or communication of prognosis creates hard-to-manage uncertainty for families and other people close to the dying person and deprives them of choices they should have had

**Programme theory ‘seed’ statements**

**Department of Health. End of Life Care Strategy, 2008**

“...”
health professionals; unnecessary costs and litigation for the health system (O multiple).

Families and other people close to the patient may also feel robbed of time and choice they feel they should have had (M/O), go through avoidable distress and traumatic experiences around the time of death (O) and be left to deal with feelings such as guilt and complicated grief for years to come (O).

She also struggled with the decision about informing Keith’s priest, as she did not want to alarm her husband but at the same time she knew he would wish to see a priest. She also felt upset and cheated that she had not been able to say goodbye to her husband before he was re-ventilated.” (p. 25)

House of Commons Health Committee report, 2015

“The decisions made by healthcare professionals about a patient’s care are often made with the best intentions and to try to ensure the highest care quality. However, in cases where decisions are made without the opportunity for the patient and their family to have their preferences assessed fairly, the patient ends up feeling distressed by their lack of choice, and that they have received a poor service.” (p. 24; evidence provided by The Parliamentary and Health Service Ombudsman)

(A, M, O) Lack of timely identification leads to delayed referrals to specialist care. As a result, patients cannot be provided with optimal support. This is also frustrating for PEoLC practitioners.

Framing sections evidence/ statement

Mintzer and Zagrabbe 2007

“Often, hospice is called in very late, within the last week or two of life—sometimes the last day or two—when optimal support and preparation for death cannot be provided. Such late referrals are frustrating to practitioners who deal with end-of-life care.”
1.3. Limitations of knowledge, skills and information as a core reason for delayed identification

<table>
<thead>
<tr>
<th>A, C, M, O</th>
<th>Original programme theory</th>
</tr>
</thead>
<tbody>
<tr>
<td>A, C, M, O</td>
<td>Department of Health 2008</td>
</tr>
<tr>
<td>A, C, M, O</td>
<td>House of Commons 2015</td>
</tr>
</tbody>
</table>

- Delays and omissions in identifying patients who may be approaching the end of their lives (A tail/O intermediate) are often a matter of insufficient training in palliative and end of life care (M), insufficient experience (M), insufficient knowledge of/ information about a particular patient shared by other colleagues within the health system (M).

- They are also more likely in diseases other than cancer (C), as their disease trajectories are less predictable (M).

- Failures of identification often result from the lack of knowledge, skills and training of staff.

- Identification of end of life stage is much easier in cancer and, respectively, challenges of identification are more likely in other conditions.

- “Many of those who provided written evidence to this inquiry expressed the opinion that health care staff need support to develop their competence in identifying, providing care to and communicating with people at the end of life and their families and carers.” (p. 20)
the last few weeks or months of life. Others will experience a more gradual decline, interspersed with episodes of acute ill health from which they may, or may not, recover. A third group are very frail for months or years before death, with a steady progressive decline.

3.4 These three patterns, or trajectories, are illustrated in Figure 1 [Note, the review team – not shown here]. Some authors have suggested that the first pattern may be typical of cancer, the second may be typical for people with organ failure (e.g. those with heart failure or chronic obstructive pulmonary disease), and the third may be typical for people with dementia.

3.5 However, empirical evidence from a cohort of patients who died of a variety of conditions over a two year period indicates that the picture is more complex (Figure 2).” (pp. 45-7)

“The trajectories of different conditions do, however, vary. The predictability of prognosis towards the end of life is generally somewhat greater for cancer than for other conditions.” (p. 97)

House of Commons Health Committee report, 2015

“The British Medical Journal has described three distinct illness trajectories for people with progressive chronic illnesses:

• a trajectory with steady progression and usually a clear terminal phase; mostly cancer
• a trajectory with gradual decline, punctuated by episodes of acute deterioration and some recovery, with more sudden, seemingly unexpected death; for example, respiratory and heart failure
• and a trajectory with prolonged gradual decline; typical of frail elderly people or people with dementia.” (p. 13)

Note, the review team: The BMJ paper referred above is the paper mentioned in the EoLC strategy (Murray S et al. 2008). This time,
however, the added complexity indicated by the Strategy (which then points to Figure 2, representing much more complex data provided by M Gott) has been lost.

“They [British Heart Foundation] note that GPs admit that introducing palliative care is fairly straightforward for people with cancer, who typically have a clear terminal decline, but much more difficult for patients with other life-threatening illnesses.” (p. 15)

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<table>
<thead>
<tr>
<th>1.4. A, C, M, O</th>
<th>Timely identification works better in theory than in practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prognostic judgements in end of life care (A) – the foundation for triggering end of life specific courses of action and services (M) –</td>
<td></td>
</tr>
<tr>
<td>are made through various combinations (M) of probabilistic objective criteria (M), professional judgement (M), and/or subjective intuitions (M)</td>
<td></td>
</tr>
<tr>
<td>using a variety of prediction modalities and frameworks (A, M) by health professionals of different professional backgrounds (C), of different levels of skills and experience (C), in different phases of an illness or frailty (C)</td>
<td></td>
</tr>
<tr>
<td>resulting in problematic prognostic accuracy (O).</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>White et al. 2016 ***</th>
</tr>
</thead>
<tbody>
<tr>
<td>White et al. 2017 ***</td>
</tr>
<tr>
<td>Downar et al 2017 ***</td>
</tr>
<tr>
<td>Bluhm et al. 2016 **</td>
</tr>
<tr>
<td>McGaughey J 2017 *</td>
</tr>
</tbody>
</table>

**O** Overall accuracy of prognosis in EoLC

White et al. 2016

*(Setting/ participants) Palliative populations and settings; “real patients” rather than hypothetical cases; English language papers.*

*(Methods) Systematic review of 42 studies on predictions of survival in palliative patients, over 12,000 prognostic estimates. Databases: MEDLINE, Embase, CINAHL, and the Cochrane Database of Systematic Reviews and Trials from inception to 2015. Papers assessed for bias (QUIPS tool) but not excluded on the basis of it.*

Distribution of percentages of accuracy for categorical survival estimates (re-organisation of data from Fig 2 of White et al., original presentation by type of categories)

<table>
<thead>
<tr>
<th>% accuracy</th>
<th>CI</th>
<th>Estimates</th>
<th>Categories</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23.3%</td>
<td>20.0-26.9</td>
<td>600</td>
<td>4</td>
<td>Llobera 2000</td>
</tr>
<tr>
<td>27.2%</td>
<td>21.7-33.2</td>
<td>243</td>
<td>8</td>
<td>Holmebakk 2011</td>
</tr>
<tr>
<td>27.3%</td>
<td>15.0-42.8</td>
<td>44</td>
<td>6</td>
<td>Glare 2001</td>
</tr>
<tr>
<td>27.6%</td>
<td>23.2-32.3</td>
<td>395</td>
<td>4</td>
<td>Fairchild 2014</td>
</tr>
<tr>
<td>30%-39%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Such challenges around the accuracy of prognosis are further exacerbated by emotional factors (M), such as reluctance to share bad news (M); perceptions of a preference, on the part of patients, to maintain hope (M); or some health professionals’ own resistance to “admitting failure” in not being able to do more for a patient (M).

<table>
<thead>
<tr>
<th>Percentage Range</th>
<th>Mean</th>
<th>95% CI</th>
<th>n</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>30.2% – 36.4%</td>
<td>35.6</td>
<td>35.1 - 36.1</td>
<td>470</td>
<td>Shah 2006</td>
</tr>
<tr>
<td>31.7% – 42.9%</td>
<td>38.2</td>
<td>36.9 - 40.0</td>
<td>82</td>
<td>Stiel 2010</td>
</tr>
<tr>
<td>31.9% – 46.7%</td>
<td>39.9</td>
<td>38.6 - 41.5</td>
<td>94</td>
<td>Bruea 1992</td>
</tr>
<tr>
<td>33.5% – 36.7%</td>
<td>35.6</td>
<td>35.0 - 36.3</td>
<td>580</td>
<td>Gripp 2007</td>
</tr>
<tr>
<td>34.0% – 36.2%</td>
<td>35.4</td>
<td>35.0 - 35.9</td>
<td>1835</td>
<td>Hui 2011</td>
</tr>
<tr>
<td>40% – 49%</td>
<td>43.5</td>
<td>42.0 - 45.1</td>
<td>273</td>
<td>Zibelman 2014</td>
</tr>
<tr>
<td>41.0% – 47.1%</td>
<td>44.5</td>
<td>43.2 - 45.9</td>
<td>237</td>
<td>Glare 2004</td>
</tr>
<tr>
<td>50% – 59%</td>
<td>54.8</td>
<td>53.4 - 56.4</td>
<td>233</td>
<td>Vigano 1999</td>
</tr>
<tr>
<td>51.5% – 69.1%</td>
<td>56.8</td>
<td>55.4 - 58.2</td>
<td>36</td>
<td>Selby 2011</td>
</tr>
<tr>
<td>55.6% – 63.6%</td>
<td>59.6</td>
<td>58.1 - 61.2</td>
<td>511</td>
<td>Brandt 2006</td>
</tr>
<tr>
<td>56.7% – 63.6%</td>
<td>60.7</td>
<td>59.2 - 62.3</td>
<td>203</td>
<td>Muers 1996</td>
</tr>
<tr>
<td>57.4% – 60.7%</td>
<td>59.7</td>
<td>58.2 - 61.3</td>
<td>987</td>
<td>Gwilliam 2013</td>
</tr>
<tr>
<td>57.6% – 62.3%</td>
<td>60.9</td>
<td>60.0 - 61.8</td>
<td>429</td>
<td>Fromme 2010</td>
</tr>
</tbody>
</table>

**Downar J et al. 2017**

*Setting/ participants* Patients with cancer (5 studies), renal failure (7), end-stage heart disease, end-stage lung disease, heterogeneous population with critical illness, a primary care practice population (1 study each). Median incidence of death for the cohorts 15.1%.

*Methods* Systematic review of 16 studies/ 17 cohorts (11 621 patients) on the Surprise Question (“Would I be surprised if this patient died in the next 12 months?”). Death at 6 to 18 months the outcome of interest. Eleven databases/ platforms searched. Overall risk of bias,
simple formulations of PPV and NVP taken from White et al. 2017 as per Quality in Prognosis Studies tool: high in 4 studies, moderate in 10 studies and low in 2 studies.

For death at 6 to 18 months, the pooled prognostic characteristics for the Surprise Question (SQ) were:

67.0% sensitivity (95% CI 55.7%–76.7%) – amongst those who died, those who were expected to die as per the Surprise Question;

80.2% specificity (73.3%–85.6%) – amongst those who survived, those who were expected to survive as per the Surprise Question;

37.1% positive predictive value (95% CI 30.2%–44.6%) – the proportion of patients who died when the clinician predicted dying;8

93.1% negative predictive value (95% CI 91.0%–94.8%) – the proportion of patients who survived when the clinician predicted survival.

“The surprise question performs poorly to modestly as a predictive tool for death, with worse performance in noncancer illness.”

“Prognostic performance was worse for noncancer illness, missing more than one third of those who died and more than two-thirds of positive results proved to be false.”

“Based on these findings, the SQ should not be used as a stand-alone prognostic tool, and we do not know whether it is more accurate for identifying patients with unmet palliative needs than it is for those in the final year of life.”

8 Simple formulations of PPV and NVP taken from White et al. 2017

White et al. 2017

(Set/ population) Patients with end-stage renal disease (8 studies), cancer (6), heart failure (4), sepsis (1), COPD (1) and variety of diagnoses (6). Patients died within the specified timeframe on 4217 occasions (16%). Country: 10 studies UK; 9 US; Germany, Hong Kong, India, Italy, Japan, New Zealand, Spain (one study each). English language publications only.

(Methods) Systematic review of 26 papers on the Surprise Question, relevant data extracted from 22 papers. 25,718 estimates. Eight databases (no retrieval from one). Quality assessed with the Newcastle-Ottawa scale; papers not excluded but appraisals used in sensitivity analysis.

Wide variation in the reported accuracy of the SQ:

- 11.6% to 95.6% – range for sensitivity
- 13.8% to 98.2% – range for specificity
- 13.9% to 78.6% – range for positive predictive value
- 61.3% to 99% – range for negative predictive value

Note, the review team: The reviews of Downar et al. 2017 and White et al. 2017 on the surprise question appear to be targeting the same papers, although one frames the review around predicting death and the other around identifying end of life patients. There are more papers and predictions in the review of White et al. 2017. Further work is needed to assess the degree of overlap in their data sources, but both reviews identify suboptimal and also variable performance of the SQ.

Note, the review team: Sources of data which can be used to assess the accuracy of predictions at a very local level include:

- evaluations of anticipatory prescribing practices;
- data from Electronic Palliative Care Coordination Systems

---

(C) Professional background, impact

White et al. 2016

*See above for brief overview of methods and setting/participants (first White et al. reference)*

No consistent evidence that one professional group or sub-group of clinicians was any more accurate than any other profession or sub-group.

(C) Experience, impact

White et al. 2016

Level of experience as improving accuracy – mixed evidence (confirmed in 2 studies, refuted 3).

(C) Multidisciplinary team working, impact

White et al. 2016

Accuracy may be better when the prognosis is made by a multidisciplinary team (2 studies).

(C) Proximity to death, impact

White et al. 2016

Time frame of the prognosis (e.g. imminent death vs. within 12 months) appeared to affect both the accuracy overall and the relative accuracy of different professionals (2 studies).

White et al. 2017
The meta-regression indicated that the increase in time frame did not impact on the diagnostic accuracy of the SQ: comparing up to 30 days with 12 months (difference in accuracy = 0.8%, 95% CI –12.8 to 14.5, \( P = 0.901 \)) and comparing up to 6 months with 12 months (difference = 4.3%, 95% CI –10.8 to 19.4, \( P = 0.561 \)).

**1.5. Ignoring the observations of low-level staff**

<table>
<thead>
<tr>
<th>C, M, O</th>
<th>Observations of patient condition made by low-level staff ignored by more senior staff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sims-Gould et al. 2010 BROADER (Canada)</td>
<td>Sims-Gould et al. 2010</td>
</tr>
</tbody>
</table>

Some staff who provide hands-on care (C) to patients may make highly accurate observations of less conspicuous changes to their condition (M), allowing them to predict a transition towards the end of life (O). However, their input is often ignored (M) and opportunities for care “switching tracks” quickly into end of life care are missed (O), as they are considered low-level personnel without the training and skills.

Nurses and healthcare assistants may be better at recognising imminent death than other professionals (2 studies).

Probabilistic estimates (4 papers) may be slightly more accurate than categorical or continuous temporal estimates of survival.

For evidence on professionals’ emotions around sharing a negative prognosis (Bluhm et al. 2016), see 2.6.1. below.
Time pressures for more senior staff (C) exacerbate the tendency to ignore what appears unimportant/unreliable as information (M).

Deliver the majority of hands-on resident care; non-clinical workers here include maintenance and support staff.

Methods Part of a broader study using “focused ethnography”. In this paper – data from 44 personal support workers (17 interviews and focus groups, unclear how many of which), and 4 non-clinical workers (4 interviews). Thematic analysis of data by three researchers, both independent work and team discussions. Findings presented to staff for validation.

“It is frustrating, and I know I’ve had an experience of people that are deteriorating really, really quickly, and [the nurses] are still telling you, ‘No, get them up, get them in the dining room,’ and you’re...in tears.”

“Yeah, you are just bottom of the barrel. What do you know about that person, you know? Even just day-to-day care, if you go and tell an RN something is different about somebody — ‘Oh, they were like that a month ago. That’s happened before.’” (p. 127)

(C) Time constraints exacerbate the tendency

“Time constraints often fracture communication or create a feeling that one’s voice or perspective is not valid or valued by others.” (p. 127)

1.6. C, M, O

Awareness of long-standing needs and PEoLC

Some terminally ill patients (cancer diagnosis) (C), whose needs for symptom control and help with self-care have been relatively long-standing (C), may be less likely to receive input from community specialist palliative nurses in the last year of life (A/O), possibly

Addington-Hall and Altmann 2000

(C, O) Association between longer-standing health needs and provision of PEoLC care

Addington-Hall and Altmann 2000

(Setting/participants) England, 20 district health authorities (self-selected but nationally representative); community specialist palliative nurses (Macmillan, hospice at home, others); by now, old data (deaths in last quarter of 1990).
due to being perceived as chronic disease patients rather than PEoLC patients (M).

Early identification of terminal phase (A) may thus, paradoxically, be associated with reduced likelihood of being prioritised for community PEoLC (M/O).

(Methods) Random sampling of 270 deaths (through death certificates) per health district, though cancer deaths sampled disproportionately due to interest of health districts (54%); semi-structured interviews with bereaved carers about the last 12 months of life; 71% response rate for cancer deaths (2074/2915).

“Patients who had had symptoms for more than 6 months were less likely to receive care from these nurses”

In logistic regression, being dependent on others for help with self-care for more than 1 year (along with four variables representing types of cancer) was associated with a decreased likelihood of receiving community specialist palliative care.

(M) Perception of patients as chronic disease rather than palliative

Addington-Hall and Altmann 2000

Authors’ explanation of pattern of data

“Patients who had had symptoms for more than 6 months were less likely to receive care from these nurses, suggesting that these patients may have been seen as falling within the rubric of chronic disease care rather than palliative care.”

1.7. C, M, O

The uncertainty of predictions may be “reverse engineered” to secure better care for patients

Lucas et al. 2008

(M, O) Revising prognosis so that it fits referral criteria to enable a patient to receive enhanced services

Lucas et al. 2008

(Setting/participants) Bradford, UK (large and deprived borough); hospice at home team covering 3 areas with a combined population of 386,000. Service targeted at patients with a prognosis of 6 weeks or
and refer a patient on the basis of a “reconsidered” (but, potentially, no less accurate) prognosis (M). Patients are thus enabled to access the services that would meet their needs (O), but which were out of bounds due to their prognosis-focused referral criteria (M).

less, irrespective of diagnosis. Practical nursing support, supplementing that provided by the patient’s own nursing team. Team composition: 1 Sister, 2 Staff Nurses, 6 Marie Curie trained Health Care Assistants, and Agency staff. Service context of high staff turnover, considerable work pressure and absence of adequate admin support.

(Methods) Data collected from Jul 2001 (inception of service) to Jun 2006. Postal questionnaire used as part of clinical audit. Respondents: carers (N eligible = 570, n sample = 289, response rate 50.7%), district nurses (n = 508, 89% response rate, no reminders) and GP’s (n = 444, 78%, no reminders). 15 questions for carers; 12 for DN’s and 3 for GP’s. Ample free-text comments, even if questionnaire did not afford it (e.g. extra pages added, written in margins). Qual data analysed using grounded theory techniques.

“Anecdotally, we identified that in some cases GPs were referring people with non-cancer diagnosis and claiming a prognosis of six weeks or less in order to give their patients access to the enhanced services hospice at home could offer. In effect the inexact science of prognosis is being used in two ways – one to exclude some people and one to include them in this sought after service even when GP’s may not have an evidence based judgement to reassure all parties that the six week prognosis was realistic. In effect the six week rule was manipulated to maximise care for individual patients.” (p. 11)
### TIMELY REFERRAL

to community PEoLC services, following or not from short prognosis/ identification of EoLC stage

<table>
<thead>
<tr>
<th>2.1. rough A, C, M, O A, C, M, O (functional equivalent, negative framing)</th>
<th>Benefits of timely (generally earlier) referral to palliative and end of life care services in the community</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timely referral to (community) PEoLC services (A) allows sufficient time for evaluating and organising care around (M) the patient and family needs, wishes, preferences and life circumstances, e.g. suitability of home for home care (M, C), and also relative to the capacity and timelines of local services (C). This enables the best possible outcomes for the patient, their family, and the sustainability of the health system (e.g. by avoiding unnecessary admissions and interventions). It also makes it more likely that the patient dies at home, if this has been their wish (O multiple). In contrast, late referrals (A late) may preclude opportunities (M) for the adequate and comprehensive assessment of needs (M), eliciting a patient’s wishes and preferences (M), arranging care in view of the above (M), as well as for the patient, family and generalist staff to benefit from highly effective, fine-tuned, flexible decisions and courses of action (M) around reducing pain and suffering and increasing quality of life (O), enabled by</td>
<td></td>
</tr>
</tbody>
</table>
| Fellowes et al. 2003 (trigger) Mintzer and Zagrabbe 2007 *
BROADER (United States) (trigger) National Institute for Health and Care Excellence guideline for service delivery, 2019 Department of Health 2008 Domain knowledge of team |
| **[A, O, C]** Timely, which is generally earlier, referral improves outcomes for cancer patients, but is unclear if this is the case for non-cancer patients **Programme theory ‘seed’ statement** |
| National Institute for Health and Care Excellence guideline for service delivery, 2019 “There is a body of research into the optimal timing of referral to specialist palliative care in cancer patients, which generally points to earlier referral leading to better patient-reported outcomes. The committee noted that similar evidence is very limited for patients with a non-cancer diagnosis, for example in patients with progressive organ failure, such as advanced heart failure, or patients with life-limiting neurological disease, such as motor neurone disease or dementia. Such patients are typically referred very late to specialist palliative care, if at all. Further research would compare outcomes for people having a combination of early identification and specialist palliative care input with those for people having usual care.” (p. 19) **[A, O] Late referrals as a source of frustration for specialists** |
| Mintzer and Zagrabbe 2007 |
the greater knowledge, skills and experience of specialist staff (M/C).

This may mean that patients endure (long) periods of preventable pain and suffering, are move vulnerable to unnecessary admissions, and/or do not have their end of life care wishes met (O multiple).

Families and other informal carers may also not receive the support they need (M/O) and, as a result, struggle with providing care (M/O), experience significant deterioration of their own health and well-being (M/O), and not be able to cope with crises in home care (M), resulting in unnecessary hospital admissions (O). After the death, they may experience feelings of guilt and complicated grief (O) and, potentially, initiate complaints against the health services (O), which had let them down (M).

Late referrals (A fail) also result in frustration for palliative and end of life care professionals (O). This is because opportunities for providing optimal care have been missed (M). Also, with the often short timelines in end of life care and often limited capacity of PEoLC services (C), specialists have not been given the chance to respond in the ways they would have wanted or were expected of them (M). This can create/ contribute to interprofessional tensions and mistrust (O/M/C).

There is, however, uncertainty whether earlier referrals, which are generally associated with better patient-reported outcomes in cancer, are similarly recommended for patients with non-cancer conditions. (C)

“Often, hospice is called in very late, within the last week or two of life—sometimes the last day or two—when optimal support and preparation for death cannot be provided. Such late referrals are frustrating to practitioners who deal with end-of-life care.”

(A, O) Late or no referrals as a source of complaints against the health system

Department of Health. End of Life Care Strategy, 2008

“[Its [of the Healthcare Commission] ‘Spotlight on Complaints’ report assessed just over a total of 16,000 complaints made about NHS organisations between July 2004 and July 2006. Approximately half of these related to care given in acute hospitals. Of these, no less than 54% related in some way to end of life care. In its latest report ‘Spotlight on Complaints 2’ (April 2008) the Commission examined 50 cases where the primary complaint was about end of life care. These complaints were mainly about poor communication, lack of basic comfort, privacy and psychological care and late or no referral for specialist palliative care. Relatives frequently commented that they seemed to be the first to recognise that the patient was dying. Inappropriate invasive procedures were often undertaken, even in the dying phase.” (pp. 24-25)

Note, the review team:

The rough theory we have described to the left includes formulations based on the background knowledge of the team which have not yet been linked to a sufficient number of illustrative sources (contents of this column). “Timely/ early vs. late referrals” at this high level of generality was de-prioritised as a potential focus for further targeted searches, as it was expected to follow a similar logic to that around timely/ early and delayed identification (1.1. and 1.2. above).
We thus focused the articulation of CMOs and associated evidence on more specific issues, as represented from 2.2. to 2.10. below.

<table>
<thead>
<tr>
<th>2.2.</th>
<th>Unclear referral criteria and/or limited awareness of them</th>
</tr>
</thead>
<tbody>
<tr>
<td>C, M, O</td>
<td>Even if generalist staff have sufficient awareness of local community PEoLC services and value them (M/C), their referral patterns may still be suboptimal (O) due to uncertainty about appropriate referral times and associated services (M).</td>
</tr>
</tbody>
</table>

Hypothesis (M), this review: Perceptions of lack of clarity of a criterion/set of criteria often relate to the need to interpret whether a particular case meets a criterion/set of criteria or not. In this sense the problem may be in the grey area of whether something counts as meeting a criterion (as would be, for instance, “end of life stage”) rather than in the lack of clear articulation and communication of relevant criteria. The solution then is not so much in clarifying the referral criteria, but in exploring the potentially sizeable grey zones of non-exemplary cases.

Fellowes et al. 2003

<table>
<thead>
<tr>
<th>(M) Uncertainty and confusion about appropriate referral times</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fellowes et al. 2003</td>
</tr>
</tbody>
</table>

(Setting/participants) UK, Marie Curie Nursing Service  
(Methods) Study-specific questionnaire to District Nurses in 37 community trusts (4 randomly selected, stratified for urban/rural, per each of the 10 Marie Curie Nursing Service districts in the UK). Questionnaires sent randomly to 40 or all (if less) DNs within a participating trust. 879 out of 1,379 surveys (64% response rate). A significant number of missing responses to some questions, but also almost 250 DNs provided additional, free-text comments.

“The MCNS [Marie Curie Nursing Service] is valued, but confusion exists about appropriate referral times and the services provided.”  
Fellowes et al. 2003  
Framing sections evidence/statement  
“However, the study also found that other health care professionals were uncertain about when they should refer people to the service. The study also found a perception within the MCNS that some referrals were inappropriate (Higginson and Wilkinson, 2002).”

Note, the review team: We do not see direct evidence in Higginson and Wilkinson 2002 to justify the interpretation of Fellows et al. but leave their claim and our challenge for further critical assessment.
<table>
<thead>
<tr>
<th>2.3.</th>
<th>M, O</th>
<th>Potential over-confidence in own knowledge of generalist staff</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Generalist staff may perceive their PEoLC knowledge and ability to deal optimally with dying patients as better than they are (M), resulting in fewer or later referrals to specialist services than beneficial for patients (O).</td>
</tr>
</tbody>
</table>

Fellowes et al. 2003

<table>
<thead>
<tr>
<th>2.3.1.</th>
<th>A, M, O (tentative hypothesis)</th>
<th>Unintended consequences of brief PEoLC training events for generalist staff?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Brief PEoLC training events for generalist staff (A) may raise confidence in own knowledge and skills more than they raise knowledge and skills (M/O). The intended outcome is that generalists are better able to look after PEoLC patients by themselves (O). This may, however, be accompanied, and potentially counterbalanced, by an unintended outcome that generalists refer to specialist care less than would be beneficial for patients (O).</td>
</tr>
</tbody>
</table>

Fellowes et al. 2003

<table>
<thead>
<tr>
<th>(M) Potential discrepancy between actual and perceived PEoLC knowledge of a significant proportion of generalist staff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fellowes et al. 2003</td>
</tr>
<tr>
<td>(Setting/ participants) UK, Marie Curie Nursing Service</td>
</tr>
<tr>
<td>(Methods, brief) Questionnaire completed by 879 District Nurses (64%).</td>
</tr>
<tr>
<td>See 2.2. for details</td>
</tr>
<tr>
<td>“It is surprising that almost 70 per cent of district nurses felt that they had sufficient expertise to provide adequate palliative care but only 13 per cent had attained a recognised palliative care qualification.”</td>
</tr>
<tr>
<td>Top reason for not referring: “able to give this patient appropriate palliative care myself”, selected “often” by 68.7% of respondents (820 responses to question).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(A, M, O) Brief PEoLC training events for generalists may have unintended outcomes on specialist referrals</th>
</tr>
</thead>
<tbody>
<tr>
<td>This review, potential explanation for pattern of data; requires further evidence</td>
</tr>
<tr>
<td>Fellowes et al. 2003 discuss the issue that almost 70% of respondents felt they had sufficient expertise to provide palliative care while only 13% had a recognised qualification in it (see immediately above). The authors, however, do not link this configuration to a further finding on training, namely that 91.8% of respondents had attended palliative or terminal care study days.</td>
</tr>
<tr>
<td>Could it be that brief training initiatives raise confidence more than they improve knowledge and skills, resulting in decisions not to refer when this would have been the best course of action? If this is, indeed, an unintended consequence observed in some cases, is its occurrence...</td>
</tr>
</tbody>
</table>
recognized by characteristics of the specialist teams (who may also be 
providing the training)?
Deprioritised for further searches.

<table>
<thead>
<tr>
<th>2.4. Family and informal carer needs as a primary reason for referring to specialist services and for the timing of the referral</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C, M, O</strong></td>
</tr>
</tbody>
</table>
| The needs of the family and informal carers may be the primary trigger for referring to specialist PEoLC community services (M). While this is an appropriate referral trigger (A), the referral might nonetheless be considered delayed (O) by specialists if the needs of the dying patient, e.g. of symptom control, are assessed by them as having required earlier expert involvement (M).

At the same time, some families may have declined earlier offers of involvement of specialist PEoLC community services (M/C), constraining the referral choices of generalist staff (O).

| Fellowes et al. 2003 |
| **(M) Family and carer needs as the primary trigger for referrals to specialist PEoLC community services** |
| Fellowes et al. 2003 |
| **(Setting/ participants) UK, Marie Curie Nursing Service** |
| **(Methods, brief) Questionnaire completed by 879 District Nurses (64%).** |
| See 2.2. for details |
| **Factors impacting on family or carers** |
| **Factors impacting on family or carers** |
| Factors impacting on family or carers |
| Anxiety/ other psychological problems |
| Practical problems |
| Social problems |
| Other physical problems |
| Pain |
| Communication problems |
| **Factors that influence “often” the timing of referral** |
| **Factors that influence “often” the timing of referral** |
| Needs of family/carer |
| Stage of disease |
| Timing of referral of patient to me |
| Workload of local Marie Curie nurses |

See 2.2. for details.

<table>
<thead>
<tr>
<th>My workload</th>
<th>3.3% (819)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(C) Trajectory of family preferences of patient referral</td>
<td></td>
</tr>
<tr>
<td>Fellowes et al. 2003</td>
<td></td>
</tr>
<tr>
<td>“[A] referral at a late stage was often at the wishes of the family who did not want MCNS input earlier.”</td>
<td></td>
</tr>
<tr>
<td>“[A] significant number of district nurses stated that the patient’s and his or her family’s unwillingness to have the service was a reason for non-referral.”</td>
<td></td>
</tr>
</tbody>
</table>

### 2.5. A, C, M, O

**Terminal stage as the other primary reason for referring to specialist services**

While PEOlC community services may be targeted at patients with a broad range of needs – e.g. pain relief and symptom control while curative treatments are still ongoing, all palliative care stages, the whole last year of life, etc. (A/C), generalists may consider such services seriously only in the last few months, weeks or even days of life (M/C), potentially prompted by the growing needs for support of families and carers (M/C, see 2.4). As a result, referrals occur most often in terminal stages (O).

| (O) Referrals as occurring most often in terminal stages |
| Fellowes et al. 2003 |
| Fellowes et al. 2003 (details in 2.2; raw numbers below are for number of valid responses to a particular question) |

**Timing of referral relative to disease stage/ proximity to death (responses ‘often’)**

| Soon after diagnosis of incurable illness | 8.6% (799) |
| When palliative care needed | 47.7% (819) |
| When terminal care needed | 88.3% (849) |
| When end-stage care needed | 94.6% (857) |

| (C) Service specifications are for a far broader range of needs and a lengthier timeline |
| Fellowes et al. 2003 |
“MCNS state that the service is available for any patient with a palliative care need (Box 1), yet less than half of district nurses (47.7 per cent) said they would often consider referring patients during the palliative phase.”

(C, M, O) Interaction between terminal stage and family needs in decisions for referral

Fellowes et al., 2003

Authors’ explanation for pattern of data

“The impression given is that consideration for referral is focused on the terminal and end stages of illness. This in itself is not surprising as these are the times when patient dependency and the support needs of the carers are at their highest.”

2.6. C, M, O

Impact of the increasing availability of curative therapies

The increasing availability of curative therapies (C), and of oral preparations in particular (C), contributes to later and later referrals (O), as there is almost always a further line of therapy that can be tried (M). At the same time, only a small proportion of patients respond to such therapies (O), the gains are minimal (O), and many patients die without receiving any, or adequate, palliative care (O).

Mintzer and Zagrabbe 2007

(Broader) Increased availability of curative therapies leads to curative attempts closer and closer to the end of life. Palliative care is, as a result, delayed while the effectiveness of therapies given as second-line or beyond is limited

Mintzer and Zagrabbe 2007

(Broader) Review of the literature on antineoplastic agents from the past 10 years; review of subsample in detail – pivotal trials on newer agents in non-small cell lung cancer for effectiveness as second-line
therapy and beyond; review of the records of 50 patients with breast, lung and colon cancer.

Authors’ explanation of pattern of observations/data

An “increasingly significant cause of delayed referral: the proliferation of antineoplastic agents that are active, but only in a few of the patients who are treated”.

The authors suggest that “treatment closer to the end of life is an inevitability that is likely to increase with the increasing number of agents available”. They see the increased availability of oral preparations as likely to further the tendency.

At the same time only a small percentage of patients respond to therapies given as second-line or beyond (while it takes 6-12 weeks to assess response) (pp. 128-129)

(M/O) Curative care attempted closer to death

Mintzer and Zagrabbe 2007

Evidence from the review of records (50): “a median interval from the date of the last regimen given to date of death of 30 days, with a range of 3 days to 8 months” (p. 128)

(C) Increased availability of curative therapies

Mintzer and Zagrabbe 2007
Circa 2007 (year of publication), Mintzer and Zagrabbe identify 26 agents which were approved by the FDA in the preceding decade and have come to be used routinely for the treatment of a variety of malignancies.

National Cancer Institute 2020

As of Feb 2020, the A to Z list of cancer drugs of the National Cancer Institute (US) lists 561 approved drugs approved for cancer or conditions related to cancer (https://www.cancer.gov/about-cancer/treatment/drugs). Update, Aug 2021: the number has increased to 641.

(O) Limited effectiveness of therapies given as second-line or beyond

Note, the review team: This category of relevant evidence was prompted by actual evidence in Mintzer and Zagrabbe 2007. However, as it came from only 3 trials and the paper is now approaching 15 years since data collection, we chose to indicate it as a necessary type of evidence but not include the data.

<table>
<thead>
<tr>
<th>2.6.1.</th>
<th>A, C, M, O</th>
<th>Non-palliative professionals as responding to patient wishes for further curative attempts, in the context of ever-present uncertainty and need for hope, rather than their clinical judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mintzer and Zagrabbe 2007 * BROADER (US)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bluhm et al. 2016 ** BROADER (US)</td>
<td></td>
</tr>
</tbody>
</table>

(C, M, O) Attempts at curative treatment are frequently made following the desires of patients and families rather than an oncologist’s best judgement, yet are still meaningful in the context of ever-present uncertainty and maintaining hope in those who need it.

Mintzer and Zagrabbe 2007

Anecdotal evidence from personal experience that it is often patients and families that desire to try out other treatments, even when these are not recommended by the oncologist.
perceiving death as a failure (M/C). As a result, patients are subjected to unnecessary interventions (A/O), which prolong suffering rather than life (O).

While this may be a valid line of explanation in some cases, it interacts in complex ways with a far less judgemental one:

A key driver of decisions to continue with curative treatments (A) are often the wishes of the patient and their family (M) rather than a non-palliative professional’s clinical judgement (M). At the same time, following the former is a meaningful choice in a context of increasing treatment options (C), an awareness that there is always the off-change, the 1% uncertainty, the miracle even (C), and the value of hope till the very end for some patients and families (C). Persevering with a curative course of action very close to the end of life may be further supported by a non-palliative professional’s own difficult emotions (M/C). These are often easier to manage by “doing something” and responding to the patient wishes and preferences for trying once more than by accepting that the patient is dying (M).

Bluhm et al. 2016

(Setting/ participants) US Midwest; oncologists from three types of settings: academic, private practice, and an oncology fellowship program. All participants routinely prescribed cytotoxic chemotherapy.

(Methods) Recruitment through physicians and administrators known to study team. Semi-structured face-to-face interviews with 17 oncologists. Qualitative content analysis. Reading and rereading of 3 transcripts by 2 team members, coding scheme developed on the basis of them. Line-by-line coding of the same transcripts by both team members; discussion; independent coding of transcripts 4-6; final coding scheme agreed, analysis completed by one team member.

Interview quotes (paper does not give indication of source, e.g. interview number):

“Usually I think if physicians end up treating to the death bed, which we sometimes do, it’s because the family or the patient [is] very insistent.”

“And so when the patient and their family [are] saying ‘Well, is there anything else,’ you sort of feel like who are you to close that door, [be]cause you actually don’t know with 100% certainty.”

“He’s in the ICU, he’s actively dying, and he’s telling us, ‘Please don’t stop the chemotherapy.’ You know what I mean? So his fight, that’s what made him happy. I think if we hadn’t treated him, we’d have felt better, but we might have kind of killed him in a way then, too.”

“I know a colleague who treats to the grave, and I think he tries to have these conversations with patients about end of life, but he always wants to present some hope, [be]cause you do. You want to balance reality with hope, and I think in his case, it always comes out...”
in such a way that people choose the hope side and go home with a prescription.”

**[M/C] Perceptions of oncologists as overly aggressive in their attempts for curative treatment even when palliation would have been the far better option**

Mintzer and Zagrabbe 2007

(in the context of discussing the proliferation of new therapies and the above anecdotal evidence) “Some have perceived oncologists as being overly aggressive with treatment. Often the use of chemotherapy or newer targeted therapies that, in retrospect, have been given close to the end of life is viewed as an error in judgment.” (128)

**[M/C] Curative and “do something” ethos amongst oncologists**

Bluhm et al. 2016

“I didn’t go into medicine to help people die.”

“That’s not just hard for them [patients] to handle, that’s hard for us to handle. We see that every day. We don’t want to tell somebody we can’t do anything for them. So it’s not just what they expect but also what we expect and maybe not being able to deal with the shortcomings of our practice … the bottom line is, you feel bad when you don’t have anything to offer someone.”

“Sometimes there is this urge like you have to offer something [be]cause you’re called to be the oncologist.”
"That's how we think. That's how oncologists are trained to think. They have to offer people something."

**(M/C) Oncologists' challenge of managing their own difficult emotions**

Bluhm et al. 2016

“Clinical factors take priority in determining late chemotherapy decisions when clear treatment choices exist. When clinical factors are ambiguous, emotion becomes a highly salient influence. Oncologists view late chemotherapy to be patient driven and use it to palliate emotional distress and maintain patient hope even when physical benefit is unexpected. Oncologists experience unique and difficult challenges when caring for dying patients, including emotionally draining communication, overwhelming responsibility for life/death, limitations of oncology to heal, and prognostic uncertainty. These challenges are also eased by offering late chemotherapy."

“Before I walk in the door and I know I’m going to do this, I still take a deep breath and walk in. And when I leave I still say my own little things in my head to myself, even when the shtick gets rote…. Believe me, there are times where I feel like I’m having an out-of-body experience because the things I’m saying are coming out so routinely that I almost feel like I’m listening to myself or watching myself. And seeing people’s reactions when you do that is emotionally draining no matter how many times you’ve done it, okay? It still is.”

“I see those [test results] and my stomach just turns, you know. It’s pretty emotional, it’s pretty intense in the room. You can kind of feel the heaviness, and it almost feels like every time you do this, a ton of bricks has fallen on top of you, if you let yourself go there.”
(M/C) The burden of what some oncologists perceive as ultimately their decision and responsibility of deciding when to “let” a patient die

Bluhm et al. 2016

“What depresses me is not that patients die. I know that. It is how I have to actively make the decision about when I'm going to let that happen. That's what gets so hard, year after year, after year, is being, in a way, like God. It's like looking at somebody you're taking care of for awhile, a long time sometimes, and thinking to yourself, you know what, it's just time for this guy to die. And that's a hard decision [be]cause basically it's my decision.”

(M/C) The background awareness that there is uncertainty; that the off-chance, 1%, “miracle” at the end of life has happened before and could happen again

Bluhm et al. 2016

“[I]f the crystal ball is telling me this guy is going to die in a week no matter what you do, you don’t treat him. Period. But it’s just not always that clear cut.”

“I wish I had been able to say, “Let’s not pursue chemotherapy,” but at the same time, it was just that, what if? What if, what if, what if?”

“Sometimes while people are at death’s door they get better. Maybe 1% are going to be cured and 99% will be dead in a month, but you don’t have a way of knowing that. Would you withhold it if the patient wanted it?”
"You hear the attending physicians talk about that one person who really wanted treatment and they thought, there's no way they're ever gonna benefit from this. And sure enough, their disease responds and they have control, and the lung cancer patient that you thought was gonna be dead in 2 months is now alive at 2 years. I mean they’re not many here. You can count [th]em on one hand. But there’s always that story.”

2.6.2. Discipline-specific levels of awareness of treatment options

Palliative care specialists (C) will be, typically, less aware (M) of innovative curative therapies in comparison to colleagues in the respective branches of medicine with curative goals (C). This too may result in conflict and antagonism about appropriate practices and timelines for PEOLC referrals (O/M/C).

Mintzer and Zagrabbe 2007 BROADER (US) Different levels of awareness of new curative options associated with a health professional’s specialty, also leading to interprofessional tensions

Mintzer and Zagrabbe, 2007

“Although those working in palliative care may be somewhat aware of these advances, palliative care professionals may not be aware of how many new agents have recently become available nor of the implications of these newer therapies in delaying hospice referrals.”

“Failure to recognize this phenomenon will also result in increased frustration and sometimes antagonism between oncologists and palliative care/hospice providers.”

2.7. System-level factors affecting late referral or non-referral

Referral decisions (O intermediate) may be affected by a range of factors associated with the structure and functioning of the health service and its entities (M/C):

Fellowes et al. 2003 (C, M) Contribution of ‘other’ factors to referral decisions and their timing

(M/C) Timing of preceding referral

Fellowes et al. 2003 (also in 2.2 and 2.4.)

(Setting/participants) UK, Marie Curie Nursing Service
| o referral of patient to referring health professional in the first place (or patient help seeking) (M/C); | (Methods) Study-specific questionnaire to District Nurses in 37 community trusts (4 randomly selected, stratified for urban/rural, per each of the 10 Marie Curie Nursing Service districts in the UK). Questionnaires sent randomly to 40 or all (if less) DN's within a participating trust. 879 out of 1,379 surveys (64% response rate). A significant number of missing responses to some questions, but also almost 250 DN's provided additional, free-text comments. |
| o own workload (M/C); | 34.3% of responding DN's state the time a patient has been referred to them influences their timing of referral. |
| o perceptions of workload of specialist community services (M/C); | 11.8% state that referrals are often delayed or prevented as a patient has been referred too late to them to refer onwards. |
| o lack of confidence in, or even negative perceptions of, a particular PEoLC service (M/C); | (M/C) Experiences of own and perceptions of others' workload |
| o accounting for service limitations (actual or perceived) (M/C); | Fellowes et al. 2003 |
| o concerns of overspending (M/C); | 10.6% state that workload of local Marie Curie nurses influences their timing of referral, while 3.3% state this of their own workload. |
| o technical problems with the referral system (M/C); | (M/C) Lack of confidence in PEoLC services |
| o the level of detail required at referral (M); | Fellowes et al. 2003 |
| o the use of alternative services (M/C); | 7.6% of respondents “indicated that late referral or non-referral of patients was due to the belief that the local MCNS could not provide appropriate care” |
| o the need to create a complete package of care, which means that any element in this package may, in some cases, be ‘called upon’ only if other elements are also becoming available (M/C). | (explanation for pattern of data) “The relatively small proportion of nurses who indicated they would refer patients with pain and communication problems seems to indicate a lack of confidence in the skills and knowledge of the MCNS.” |

While such factors are unlikely to affect decisions in cases where referral is clearly indicated (C), they may have decision-changing power in cases where the need for and benefit of the referral is less certain (C). Their accumulation may also reverse-engineer (M) perceptions of referral urgency (O intermediate).

The incorporation of such factors in one’s decision making (M) is likely to vary across health professionals (C), resulting in different referral

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patterns (O intermediate) across individuals and teams (C).

Importantly, overall high positive perceptions of a service (C) do not ‘switch off’ factors which delay or limit (M) referrals (O intermediate).

“There may also be a lack of awareness that all grades of MCNS staff are expected to complete a recognised qualification in palliative care on appointment and to attend regular updates.”

**[M/C] Concerns about overspending**

Fellowes et al. 2003

7.0% of respondents express concern that they would overspend on Marie Curie nurses.

“A minority of district nurses had only limited use of the MCNS, stating that ... [they] were restricted in the frequency of referral for financial reasons.”

**[M] Challenges of using referral system and processes**

Fellowes et al. 2003

9.5% of respondents reported frequent delays or obstruction of referrals due to booking system.

“Some district nurses attributed unavailability to both a shortage of nurses and to NurseLink, which they perceived as distant and inflexible in dealing with local needs.”

“A small number of respondents commented on other aspects of communication, such as ... the extent of details required at referral.”

**[M/C] Referral to other services**

Fellowes et al., 2003
<table>
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<tbody>
<tr>
<td>22.3 % of respondents reported referring to a Macmillan nurse.</td>
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<tr>
<td>“When asked for any other reasons that had prevented or delayed referral to the MCNS, the main reason given was referral to other professionals such as local services.”</td>
</tr>
<tr>
<td>(M/C) Accounting for and dissatisfaction with service limitations</td>
</tr>
<tr>
<td>Fellowes et al., 2003</td>
</tr>
<tr>
<td>46.0% reported that referrals are often delayed or prevented because the service has no capacity (no Marie Curie nurse available) when needed.</td>
</tr>
<tr>
<td>“However, district nurses expressed some dissatisfaction over the availability of the MCNS for rural areas, for holiday periods, for day care, for regular respite care, and for care at short notice.”</td>
</tr>
<tr>
<td>(M/C) The need to coordinate care provision from several services</td>
</tr>
<tr>
<td>Fellowes et al. 2003</td>
</tr>
<tr>
<td>“They also highlighted problems that arose when trying to coordinate a number of palliative care services for 24-hour care.”</td>
</tr>
<tr>
<td>“Unfortunately, Marie Curie cannot provide 24-hour care in exceptional circumstances. With help from Social Work Department and Hospice at Home, a complete package of care can be provided ... it’s very stressful for district nurses not knowing until the last minute what care can be provided, but overall the service is wonderful.” (free-text response)</td>
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<td>2.8.</td>
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</table>

Data on cancer death registrations in England for 1997, from ONS (Office of National Statistics); statistical analysis – frequency distributions, univariate analysis and multivariate analysis on predictors of not dying at home;

High level of missing data for place of death (recorded 13,311, missing for 13,321) and of these 94% died at home.

Shorter time between referral and death found to be associated with home death (OR 0.99; CI 0.99 – 0.99, narrow CI explained by high numbers in sample).

Grande et al. 2003

(Setting/ participants) Cambridgeshire, UK; cancer patients. All National Health Service home care received in the last year of life for patients who died at home vs. patients who died in inpatient care (the latter including hospital, hospice, nursing or residential home, or in transition).

(Methods) Post hoc exploratory case-control study of 127 home deaths and 200 inpatient deaths. 16-month period. One sample of patients referred to a local Hospital at Home service for palliative care (121). The other sample of patients from a local cancer registry (206). Retrospective electronic record linkage of patients’ community and inpatient care during the last year of life (robust process of identifying and matching records).

<table>
<thead>
<tr>
<th>Service type</th>
<th>Start of service as median days before death</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>District nursing</td>
<td>71 days (104)</td>
<td>141.5 days (132)</td>
</tr>
</tbody>
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BMJ Support Palliat Care
doi: 10.1136/bmjspcare-2021-003066

BMJ Support Palliat Care
Night nursing        7.5 days (32)                          26 days (17)                   p=0.001  
Macmillan              91.5 days (40)                        81.5 days (32)        non-sign  
Marie Curie            12 days (63)                           30.5 days (30)                 p=0.008  
Other community trust care  38 days (19)                           58 days (18)        non-sign  
Flexible care         20 days (18)                           50.5 days (12)        non-sign  
Hospital@Home nursing  6 days (51)                           21 days (10)                    p=0.005  

For inpatient services, data on inpatient hospice care show, in contrast, that starting care earlier is associated with home death (median of 35 days for the patients who died at home and 12 days for the patients who died as inpatients). Receiving care from the specialist hospital teams also shows a tendency towards increasing likelihood of home death (p=0.07)

Explanation of pattern of data

“Patients who began their home nursing early were less likely to die at home than those who began such care late. This suggests that it may be difficult to sustain end-of-life care at home for an extended period.”

“This may be due to the strain this places on informal care resources, as family carers shoulder the greater part of the burden.”

2.10. Earlier and later referral relative to time of diagnosis

At least in cancer patients (C), later referral to a palliative care physician relative to the time of diagnosis (A) may increase the likelihood that a

Maida 2002

BROADER (Canada)

(A-O association) Longer time between diagnosis and referral and likelihood of home death

Maida 2002
<table>
<thead>
<tr>
<th>Patient dies at home (O). This may be because they have developed greater acceptance of their terminal prognosis (M/C) and/or because they have been “through more trials, tribulations, and treatment failures, and spent more time in institutions” (M/C). They may thus be more likely to seek, accept and plan for home-based palliative care as opposed to more invasive, hospital-based care with curative or life-prolonging goals (M).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(Setting/ participants)</strong> Combined community and hospital-based palliative care service in Toronto, Ontario, Canada. Patients residing in five districts of metropolitan Toronto, within 20 km radius of base hospital. Referrals made by oncologists, surgeons and general practitioners. Patients seen initially within 24 hours of referral. Around the clock on-call coverage by the palliative care physicians (unclear if only at home). All patients receive regularly scheduled RN visits. Patients aware of terminal diagnosis and expressed a preference to die at home.</td>
</tr>
<tr>
<td><strong>(Methods)</strong> Retrospective chart review (both medical and nursing charts) of 402 sequential cancer patients referred to service. Period between 1 Apr 1997 and 8 Apr 1999 (24 months). Further information collected at visits (e.g. number of caregivers) or from web-based sources (Toronto Real Estate Board’s web-service for home valuation). Analysis in SAS, both parametric and non-parametric.</td>
</tr>
<tr>
<td>Mean number of months between diagnosis and referral: 27.3 months, SD 2.34 for those who died at home vs. 11.6, SD 2.61 for those who died at hospital; p &lt; 0.001. (Note it is not months before death, but between diagnosis and referral, i.e. potential “delay” in referral)</td>
</tr>
<tr>
<td><strong>(M/C) Period of time since diagnosis in relation to acceptance of death and desire to avoid the downsides of treatment</strong></td>
</tr>
<tr>
<td>Maida 2002</td>
</tr>
<tr>
<td>(explanation of pattern of data) Longer period of time between diagnosis and referral to palliative care physician means that such patients will have lived “with the knowledge and ramifications of their condition for longer”. This has given them the opportunity to develop greater acceptance of their terminal prognosis. Such patients have, overall, also gone “through more trials, tribulations, and treatment failures, and spent more time in institutions”. Perhaps they had a greater desire to return home finally to die. (p. 285)</td>
</tr>
</tbody>
</table>
3. Supplementary Table 2: Abstract-level scoping of systematic reviews on prognosis from the last 5 years (2015-2020)

This table includes core information from a scoping search on recent research on prognosis, relative to expectations that advancements in research can point towards better prognostic tools/approaches for identifying patients at the end of life.

The search strategy is described in the Literature searching appendix (Appendix 4). We have included abstracts of papers published between 2015 and 2020. We excluded: non-systematic reviews (e.g. narrative reviews or supposedly systematic reviews using a single database); research on children; papers on procedures with curative intent and/or exclusive focus on longer survival timeframes (e.g. 5 or 10 years). In cases where overall survival at 5 or 10 years was rather low, e.g. below 20%, we did, however, include the papers. We excluded studies we have already reported on in the CMO table above.

For the needs of this preliminary scoping search, we only accessed the abstracts of papers. If the paper had no abstract or it did not provide sufficient information about its findings, it was not added to the table.

Some frequent abbreviations in the authors’ abstracts are:

OS – overall survival
DFF – disease free survival
PFS – progression free survival
RFS – relapse free survival
DSS – disease specific survival
<table>
<thead>
<tr>
<th>Reference (authors and year)</th>
<th>Condition, condition + therapy, or setting</th>
<th>No studies reviewed</th>
<th>No participants</th>
<th>Predictors of survival or predictive approach explored</th>
<th>Findings</th>
<th>Broad conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Bu et al. 2015</td>
<td>malignant tumors</td>
<td>30</td>
<td>4497</td>
<td>MicroRNA-126</td>
<td>“High level of miR-126 was a predictor for favorable survival of carcinomas, with pooled HR of 0.77 (95% CI 0.64-0.93) for OS, 0.64 (95% CI 0.48-0.85) for DFS, and 0.70 (95% CI 0.50-0.98) for PFS/RFS/DSS.” “However, high level of circulating miR-126 predicted a significantly worse OS in patients with cancer (HR = 1.65, 95% CI 1.09-2.51).”</td>
<td>Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed, but opposing valence depending on context</td>
</tr>
<tr>
<td>2. Li et al. 2015</td>
<td>non-small cell lung cancer</td>
<td>10</td>
<td></td>
<td>rapamycin (mTOR) and phosphorylated mTOR (p-mTOR)</td>
<td>“The results indicated that no statistically significant association was found between mTOR/p-mTOR expression and NSCLC patients’ prognosis.”</td>
<td>No/insufficient/weak evidence</td>
</tr>
<tr>
<td>3. Petrelli et al. 2015</td>
<td>survival with bevacizumab-based therapy in colorectal cancer patients</td>
<td>29</td>
<td>11,585</td>
<td>Potential prognostic factors in 3 or more source papers (see column to the right)</td>
<td>Five parameters were associated with survival in &gt;3 papers: (1) a longer progression-free interval [PFS: HR 0.87, 95% confidence interval (CI) 0.78-0.97; P = 0.01]; (2) a single site of metastases (HR 0.63, 95% CI 0.56-0.71; P &lt; 0.00001);</td>
<td>Prognostic/predictive value of small set of parameters confirmed, highly specific context of condition and/or therapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. Qi et al. 2015</th>
<th>Budd-Chiari syndrome</th>
<th>79 studies</th>
<th>Median 1-year survival rate: 93% after interventional radiological treatment, 81% after surgery other than liver transplantation, 82.5% after liver transplantation, 68.1% after medical therapy alone. “Bilirubin, creatinine and ascites were more frequently identified as significant prognostic factors in univariate analyses. But their statistical significance was less frequently achieved in multivariate analyses.”</th>
<th>No/ insufficient/ weak evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>5. Tang et al. 2015</td>
<td>Breast cancer</td>
<td>41 articles</td>
<td>MicroRNAs (miRNAs) – 27 types, as identified in the source studies, with “For the studies evaluating miR-21’s association with clinical outcomes, the median HR in the studies was 2.32 (interquartile range [IQR] = 1.04-3.40), and the pooled HR suggested that high expression of miR-21 has a negative</td>
<td>Single marker (i.e. relative importance unclear), prognostic/</td>
</tr>
</tbody>
</table>
micRNA-21 (miR-21) studied most often impact on overall survival (OS; HR = 1.46, 95% CI, 1.25-1.70; p<0.05) and disease/recurrence-free survival in breast cancer (HR = 1.49, 95% CI, 1.17-1.90; p<0.01)."

"We also found that higher expression levels of miR-210 significantly predicted poorer outcome, with median HR in the reported studies of 4.07 (IQR = 1.54-4.43) and a pooled HR of 2.94 (95% CI, 2.08-4.17; p<0.05)."

6. Thuy et al. 2015 Glioblastoma multiforme (GBM) 14,678 39 unique genetic or molecular factors A few hundred genetic and molecular predictors have been implicated in the literature, however with the exception of IDH1 and O6-MGMT, there is uncertainty regarding their true prognostic relevance.

Seventy-four random effects meta-analyses were performed on 39 unique genetic or molecular factors.

(no further findings reported in abstract)

Multiple (>30) prognostic/predictive factors, findings unclear from abstract

7. Wang et al. 2015 cancer 15 2,597 MicroRNA-34a (miR-34a) "Overexpression of miR-34a may predict good overall survival ([OS), HR =0.76, 95% confidence interval: 0.55-1.06, P=0.105], but the effect was not significant enough. Subgroup analysis results showed miR-34a was an ideal predictor for digestive system cancer (OS, HR =0.50, 95% confidence interval: 0.25-0.99, P=0.048). The predictive effects of elevated expression of miR-34a on the OS of untreated and treated patients were not of obvious differences."

Single marker (i.e. relative importance unclear), weak evidence for overall predictive/prognostic value, strong evidence for a specific context

8. Wei and Niu 2015  Various cancers  9  932  metastasis-associated lung adenocarcinoma transcript 1 (MALAT1)  "Elevated MALAT1 expression was significantly correlated with poor OS (HR 2.02; 95% CI: 1.62-2.52; P < 0.001; I(2) = 0%). Subgroup analysis indicated that tumor type, histology type, ethnicity, and measurement technique did not affect the prognostic value of MALAT1 for OS. The HR of elevated MALAT1 for DFS was 2.78 (95% CI: 1.87-4.15; P < 0.001; I(2) = 0%)."  Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed

9. Zhou C et al. 2015  patients with liver diseases who have undergone transjugular intrahepatic portosystemic shunt (TIPS)  11  Comparison of the Child-Turcotte-Pugh (CTP) score and the model for end-stage liver disease (MELD) score for predicting survival in such patients  "In the meta-analyses, MELD score was superior to CTP score in predicting 3-month survival after TIPS (mean ES, 0.63; 95% confidence interval [CI], 0.13-1.14; P=0.01), but the predictive capability in 1-month, 6-month, and 12-month survival was not significant (1-month: mean ES, 0.79; 95% CI, -0.24-1.83; P=0.13; 6-month: mean ES, 0.46; 95% CI, -2.46-3.37; P=0.76; 12-month: mean ES, 0.36; 95% CI, -0.25-0.96; P=0.25). CONCLUSIONS: No enough evidence are confirmed so far that MELD score is better than CTP score to assess the overall prognosis after TIPS, especially long-term predictions, but 3-month predictive capability of MELD score significantly outperform CTP score."

10. Cheon et al. 2016  Advanced cancer  15  Clinicians' predictions of survival  "Clinicians in five studies underestimated patients' survival (estimated to observed survival ratio between 0.5 and 0.92). In contrast, 12 studies reported clinicians' overestimation of survival (ratio between 1.06 and 6)."

"CPS in advanced cancer patients is often inaccurate and overestimated." Inaccuracy of clinician predictions

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<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Setting</th>
<th>Marker</th>
<th>Description</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>11. Lee et al. 2016</td>
<td>Early-stage endometrial cancer</td>
<td>Positive peritoneal cytology</td>
<td>“In patients with surgical stage 1 or 2 early-stage endometrial cancer, the incidence of Grade 3 was higher and 5-year overall survival was worse in patients with positive peritoneal cytology compared with negative peritoneal cytology. However, the incidence of Grade 1 was lower in those with positive peritoneal cytology compared with negative peritoneal cytology. In patients with surgical stage 1 early-stage endometrial cancer, the incidence of myometrial invasion &gt;=1/2 tended to be higher and 5-year progression-free survival was worse in the positive peritoneal cytology group than the negative peritoneal cytology group. However, the incidence of myometrial invasion &lt;1/2 was lower in the positive peritoneal cytology group than the negative peritoneal cytology group.”</td>
<td>Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed, but opposing valence depending on context</td>
</tr>
<tr>
<td>12. Leuzzi et al. 2016</td>
<td>Non-small-cell lung cancer (NSCLC)</td>
<td>Baseline C-reactive protein (CPR)</td>
<td>“In overall analysis, elevated pretreatment CRP values were significantly associated with poor overall survival (HR 1.60, 95% CI 1.30-1.97, p&lt;0.001, I2 = 71.9%). Similar results were observed across considered strata. However, higher mortality risk was reported in studies in which CRP was combined with other factors (HR 1.96, 95% CI 1.58-2.45) and in those using a cutoff value of 3 mg/L (HR 1.89, 95% CI 1.52-2.35). CONCLUSIONS: Based on our analysis, baseline high CRP level is significantly associated with poor prognosis in early-stage NSCLC. Further prospective controlled studies are needed to confirm these data.”</td>
<td>Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed, further research recommended</td>
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<tr>
<td>13.</td>
<td>Marques et al. 2016</td>
<td>Head and neck cancer</td>
<td>12</td>
<td>mTOR pathway protein immunoexpression</td>
</tr>
<tr>
<td>14.</td>
<td>Qian et al. 2016</td>
<td>Systemic lupus erythematosus (SLE)-associated pulmonary arterial hypertension (PAH)</td>
<td>6</td>
<td>323</td>
</tr>
<tr>
<td>15.</td>
<td>Shan et al. 2016</td>
<td>Cancer</td>
<td>44</td>
<td>Dicer status</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cancer Type (16)</th>
<th>Tumor Types (18)</th>
<th>HMGB1 Overexpression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu et al. 2016</td>
<td>11 different tumor types</td>
<td>High mobility group box 1 (HMGB1) overexpression</td>
</tr>
</tbody>
</table>

HMGB1 overexpression was significantly associated with poorer OS (HR: 1.99; 95% CI, 1.71-2.31) and PFS (HR: 2.26; 95% CI, 1.65-3.10) irrespective of cancer types including gastric cancer, colorectal cancer, hepatocellular carcinoma, pancreatic cancer, nasopharyngeal carcinoma, head and neck squamous-cell carcinoma, esophageal cancer, malignant pleural mesothelioma, bladder cancer, prostate cancer, and cervical carcinoma. Subgroup analyses indicated geographical area and size of studies did not affect the prognostic effects of HMGB1 for OS. Moreover, HMGB1 overexpression had a consistent correlation with poorer OS when detected by immunohistochemistry in tissues and enzyme-linked immunosorbent assay in serum, whereas the correlation did not exist by quantitative real-time reverse-transcription polymerase chain reaction in tissues. HMGB1 overexpression is associated with poorer prognosis.

CONCLUSION: Low Dicer status was associated with poor prognosis in ovarian cancer, otolaryngological tumors and hematological malignancies. More homogeneous studies with high quality are needed to further confirm our conclusion and make Dicer a useful parameter in clinical application.”

Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed.
<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Sample Size</th>
<th>Method</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>17. Chen et al. 2017</td>
<td>cancer</td>
<td>7</td>
<td>652</td>
<td>Long noncoding RNA HOTTIP - HOXA transcript at the distal tip (HOTTIP), a functional lncRNA transcribed from the 5' tip of the HOXA locus. &quot;The results showed a significant positive association between HOTTIP levels and LNM (Odds ratio, OR = 2.30, 95% CI: 1.58-3.35, p &lt; 0.0001) in a fixed-effects model (I² = 0%, p = 0.949) and it could also predict poor OS in cancer patients (Hazard ratio HR = 2.24, 95% CI: 1.74-2.90, p &lt; 0.0001) in a fixed-effects model (I² = 0%, p = 0.925). In conclusion, this meta-analysis demonstrated that the higher expression level of HOTTIP is correlated with positive LNM and poor OS in different types of cancer and HOTTIP might serve as a novel predictor of LNM and survival in human cancer.&quot; LNM = lymph node metastasis.</td>
</tr>
<tr>
<td>18. Mahar et al. 2017</td>
<td>Colorectal cancer</td>
<td>Clinical prognostic tools for survival outcomes</td>
<td>Significant heterogeneity in colorectal cancer prognostication tool quality exists. Methodology is incompletely or inadequately reported. Evaluations of the internal or external validity of the prognostic model are rarely performed. Prognostication tools are important devices for patient management, but tool reliability is compromised by poor quality. Guidance for future development of prognostication tools in colorectal cancer is needed.</td>
<td>Tools (scores, indices) – inconsistent or poor performance.</td>
</tr>
<tr>
<td>19. Nater et al. 2017</td>
<td>symptomatic spinal metastasis (SSM)</td>
<td>17</td>
<td>46 predictors of survival identified</td>
<td>The strength of the overall body of evidence was very low for 39 and low for 7 predictors.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Disease</th>
<th>Location or Organ</th>
<th>HRQoL Outcomes in Surgical Patients with SSM</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>20. Petrelli et al. 2017 JAMA Oncology</td>
<td>Colon cancer</td>
<td>66</td>
<td>1437846</td>
<td>“Left sided primary tumor location was associated with a significantly reduced risk of death (HR, 0.82; 95% CI, 0.79-0.84; P &lt; .001) and this was independent of stage, race, adjuvant chemotherapy, year of study, number of participants, and quality of included studies.” Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed</td>
</tr>
<tr>
<td>21. Petrelli et al. 2017 Urology</td>
<td>Radical nephroureterectomy for upper urinary tract urothelial carcinoma</td>
<td>Prognostic factors that influence overall survival described in the literature</td>
<td>“The clinicopathological factors associated with an increased risk of death were age, multifocality, lymphovascular invasion, pT3-4 stage, pT2 vs &lt;pT2 stage, node-positive disease, tumor grade, tumor size, and positive surgical margins.” Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed</td>
<td></td>
</tr>
<tr>
<td>22. Smith et al. 2017</td>
<td>COPD</td>
<td>10</td>
<td>known prognostic variables and scores that predict prognosis in COPD, specifically including variables that contribute to risk assessment of patients for death within 12 months</td>
<td>“No multivariable indices were developed with the specific aim of predicting all-cause mortality in stable COPD within 12 months. Only nine indices were identified from four studies, which had been validated for this time period. Tools developed using expert knowledge were also identified, including the Gold Standards Framework Prognostic Indicator Guidance, the RADboud Indicators of Palliative Care Needs, the Supportive and Palliative Care Indicators Tool and the Necesidades Paliativas program tool. CONCLUSION: A number of variables contributing to the prediction of all-cause mortality in COPD were identified. However, there are very few studies that are designed to Tools (scores, indices) – unspecific</td>
</tr>
<tr>
<td>Study (Year)</td>
<td>Type of Cancer</td>
<td>Sample Size</td>
<td>Predictive Markers</td>
<td>Findings</td>
</tr>
<tr>
<td>-------------</td>
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</tr>
<tr>
<td>Urun et al. 2017</td>
<td>Advanced urothelial cancer treated with platinum-based chemotherapy</td>
<td>13/1475</td>
<td>Excision repair cross-complementing group 1 (ERCC1)</td>
<td>ERCC1 positivity was significantly associated with worse progression-free survival (pooled HR: 1.54, 95% CI: 1.13-2.11, p=0.006). There was no significant association with overall survival (pooled HR: 1.63, 95% CI: 0.93-2.88, p=0.09) and disease-free survival (pooled HR: 1.09, 95% CI: 0.63-1.90, p=0.75).</td>
</tr>
<tr>
<td>Yang et al. 2017</td>
<td>Epithelial ovarian cancer</td>
<td>12/3,154</td>
<td>Neutrophil-to-lymphocyte ratio (NLR)</td>
<td>Elevated NLR in EOC patients was associated with worse PFS (summarized HR=1.80; 95% CI=1.22-2.65; I²=79.1%) and OS (summarized HR =1.72; 95% CI=1.18-2.51; I²=73.5%) compared with low NLR. No evidence of publication bias was detected by funnel plot analysis and formal statistical tests. Although the results were robust in all subgroup analyses, not all results were statistically significant. We determined that adjustments for CA-125 level and performance status might be sources of heterogeneity. These combined results indicate that preoperative NLR is an important predictor of prognosis in EOC patients. Since the high heterogeneity and retrospective study design of included studies, these results require further validation with prospective cohort and trials enrolling larger patient populations and conducting longer follow-up examinations.</td>
</tr>
<tr>
<td>25. Zabaleta et al. 2017</td>
<td>Pulmonary metastasectomy in colorectal cancer patients</td>
<td>28</td>
<td>History of resected liver metastases</td>
<td>&quot;In more than half of the papers analyzed (63.2%), patients with a history of resected liver metastases had a lower survival rate than those who did not have such a history, and the difference was statistically significant in eight of these studies. However, data were presented differently, and authors reported mean survival time, survival rates, or hazard ratios. CONCLUSIONS: A history of liver metastases seems to be a negative prognostic factor, but the individual data need to undergo a meta-analysis.&quot;</td>
</tr>
<tr>
<td>26. Zhang et al. 2017</td>
<td>Colorectal cancer</td>
<td>23</td>
<td>Metabolomic profile of patients</td>
<td>&quot;Metabolites related to cellular respiration, carbohydrate, lipid, protein and nucleotide metabolism were significantly altered in CRC. Altered metabolites were also related to prognosis, survival and recurrence of CRC. This review could represent the most comprehensive information and summary about CRC metabolism to date. It certifies that metabolomics had great potential on both discovering clinical biomarkers and elucidating previously unknown mechanisms of CRC pathogenesis.&quot;</td>
</tr>
<tr>
<td>27. Zhao et al. 2017</td>
<td>Pulmonary metastasectomy in renal cell cancer patients</td>
<td>16</td>
<td>Prognostic factors as identified in the literature</td>
<td>&quot;The poor prognostic factors were lymph node involvement (LNI) of primary RCC (HR 3.44, 95% confidence interval (CI) 1.78-6.67, P = 0.001), incomplete resection of metastases (HR 3.74, 95% CI 2.49-5.61, P = 0.000), multiple metastases (HR 1.55, 95% CI 1.18-2.03, P = 0.002), larger metastases (HR 1.45, 95% CI 1.26-1.66, P = 0.000), LNI of metastases (HR 3.06, 95% CI 1.52-6.19, P = 0.002), synchronous</td>
</tr>
<tr>
<td>Sample Size</td>
<td>Prognostic Factor</td>
<td>Prognostic Analysis</td>
<td>Conclusion</td>
<td></td>
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<tr>
<td>28. Bollen et al. 2018</td>
<td>Spinal bone metastases</td>
<td>A total of 43 different prognostic factors were investigated in the included studies, of which 17 were relevant to pre-treatment survival estimation.</td>
<td>The prognostic factors most frequently associated with survival were the primary tumor and the performance status. The prognostic factors most frequently not associated with survival were age, gender, number and location of the SBM and the presence of a pathologic fracture. Conclusions: Prognostication for patients with SBM should be based on an accurate primary tumor classification, combined with a performance score. The benefit of adding other prognostic factors is doubtful.</td>
<td></td>
</tr>
<tr>
<td>29. Bosma et al. 2018</td>
<td>Ewing sarcoma</td>
<td>24 prognostic factors were investigated, 14 relevant for this review</td>
<td>Prognostic factors associated with survival include metastasis at diagnosis, large tumors (volume&gt;=200ml or largest diameter&gt;=8cm), primary tumors located in the axial skeleton, especially pelvic and a histological response of less than 100%. These factors should be included as risk factors in the development of prediction models for ES.</td>
<td></td>
</tr>
<tr>
<td>30. Chi et al. 2018</td>
<td>cancer</td>
<td>albumin to globulin ratio (AGR)</td>
<td>The analysis based on random-effect model demonstrated that low AGR was significantly associated with poor OS in various cancers (HR=1.87, 95% CI 1.50-2.34; P &lt; 0.001). “A large scale of samples and prospective studies are needed in the future to validate the role of AGR in practice.”</td>
<td></td>
</tr>
</tbody>
</table>


Familiar parameters validated from a large number of candidates

Prognostic/predictive value of small set of parameters confirmed, highly specific context of condition and/or therapy

Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed, further research recommended
| 31. Dan et al. 2018 | cancer | 11 | 1,797 | miR-375 | “The pooled HR for overall/cumulative survival (OS/CS) was 1.90 (95% confidence interval (CI) 1.57-2.29) and the pooled HR for disease-free, recurrence-free or progression-free survival (DFS/RFS/PFS) was 1.93 (95% CI 1.39-2.67), indicating low miR-375 expression was associated with significantly poorer outcomes compared to normal/high miR-375 expression. Subgroup analysis revealed miR-375 might be a good prognostic factor in cancer, regardless of population, sample type, and cancer type. The prognostic value of miR-375 in non-Chinese patients was particularly high (pooled HR > 2). CONCLUSION: Low miR-375 expression could represent a valuable prognostic marker in various cancers. Circulating miR-375 levels may provide a useful non-invasive, practical prognostic biomarker. However, the prognostic value of miR-375 in specific cancer types remains unclear; further studies are warranted.” | Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed, further research recommended |
| 32. Georgakis et al. 2018 | Gliomatosis cerebri (GC) | 523 patient level data | | | The median OS and PFS were 13 and 10 months, with 5-year rates of 18% and 13%, respectively. 
Age >=65 years at diagnosis (hazard ratio for OS \( \text{HR}_{\text{OS}} \), 2.32; 95% confidence interval \( \text{CI} \), 1.62-3.31), 
high-grade tumor (HR\( \text{PFS} \) for grade III, 1.57; 95% CI, 1.02-2.40; HR\( \text{PFS} \) for grade IV, 1.74; 95% CI, [0.98-3.10]), | Prognostic/predictive value confirmed (16 factors) |
| GC type II (HR<sub>OS</sub>, 1.49; 95% CI, 1.12-1.98; HR<sub>PFS</sub>, 1.56; 95% CI, 1.04-2.34), |
| more central nervous system (CNS) regions involved (HR<sub>OS</sub>, 1.09; 95% CI, 1.01-1.18), |
| focal neurological deficits (HR<sub>OS</sub>, 1.41; 95% CI, 1.07-1.86), |
| cerebellar symptoms (HR<sub>PFS</sub>, 2.20; 95% CI, 1.42-3.39), |
| more symptoms at presentation (HR<sub>OS</sub>, 1.21; 95% CI, 1.05-1.40), |
| Karnofsky performance scale score <70 (HR<sub>OS</sub>, 3.58; 95% CI, 1.73-7.39; HR<sub>PFS</sub>, 4.48; 95% CI, 1.39-14.4), |
| magnetic resonance imaging contrast enhancement (HR<sub>OS</sub>, 1.48; 95% CI, 1.12-1.96; HR<sub>PFS</sub>, 1.74; 95% CI, 1.18-2.55), |
| symmetric bilateral CNS invasion (HR<sub>OS</sub>, 1.42; 95% CI, 1.03-1.96), |
| and high proliferation index (Ki-67 >5%; HR<sub>OS</sub>, 2.32; 95% CI, 1.11-4.86) |
| were independent predictors of poor outcomes. |

In contrast,
 seizure occurrence (HR\textsubscript{OS}, 0.77; 95% CI, 0.60-1.00; HR\textsubscript{PFS}, 0.68; 95% CI, 0.47-0.95),

isocitrate dehydrogenase 1 mutation (HR\textsubscript{OS}, 0.16; 95% CI, 0.05-0.49),

and O6-methylguanine-DNA-methyltransferase promoter methylation (HR\textsubscript{OS}, 0.23; 95% CI, 0.09-0.59) were associated with prolonged survival.

Chemotherapy and surgical resection were associated with improved outcomes, but radiotherapy, whether monotherapy or combined with chemotherapy, was not superior to chemotherapy alone.

<p>| 33. Huang et al. 2018 | Lung cancer | 55 | 22,719 | decreased pretreatment haemoglobin level | &quot;The results indicated that decreased haemoglobin level was significantly associated with poor overall survival of patients with lung cancer (HR 1.51, 95% CI 1.42-1.61), both in non-small cell lung cancer (HR 1.57, 95% CI 1.44-1.72) and in small cell lung cancer (HR 1.56, 95% CI 1.21-2.02). We also found that the lower the haemoglobin level, the shorter was the overall survival of patients with lung cancer (HR 1.11, 95% CI 1.06-1.16).&quot; | Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed |
| 34. Kloter et al. 2018 | cancer | 19 | Heart rate variability | &quot;[H]igher HRV correlated positively with patients' progression of disease and outcome. Thus, we conclude that individuals with higher HRV and advanced coping mechanisms seem to have a better prognosis in cancer progression.&quot; | Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed |</p>
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Type</th>
<th>Patients</th>
<th>N</th>
<th>Setting</th>
<th>Marker</th>
<th>Description</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lakshminarayana et al. 2018</td>
<td>Oral squamous cell carcinoma (OSCC)</td>
<td>36</td>
<td>Molecular pathways and genes involved in oral cancer</td>
<td>Three major interlinked pathways found were the nuclear factor kappa B (NF-κB), PI3K-AKT, and Wnt pathways. The commonly mutated genes were cyclin D1 (CCND1), Rb, p53, FLJ10540, and TC21. The NF-κB, PI3K-AKT, and Wnt pathways are most frequently involved in the molecular pathogenesis of oral cancer. However, the CCND1, Rb, p53, FLJ10540, and TC21 genes were found to be more accurate in determining patients’ overall survival.</td>
<td>Prognostic/predictive value confirmed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li et al. 2018</td>
<td>Gastric cancer</td>
<td>8</td>
<td>950</td>
<td>Expression of VEGFRs</td>
<td>The combined HR of studies evaluating total VEGFRs overexpression was 1.42 (95% CI 1.01-2.00, P=0.044), suggesting that it had prognosis significance in overall survival of gastric cancer. Subgroup analysis showed that it was VEGFR-2 (HR 1.81, 95% CI 1.31-2.49, P&lt;0.001) but not VEGFR-3 (HR 0.91, 95% CI 0.45-1.82, P=0.787) overexpression was associated with an increased risk of median overall survival (mOS) and it can be a potentially predictive biomarker for gastric cancer.</td>
<td>Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed</td>
<td></td>
</tr>
<tr>
<td>Liu et al. 2018</td>
<td>Patients in palliative care</td>
<td>15</td>
<td>7455 assessments</td>
<td>Palliative prognostic index (PPI)</td>
<td>Four studies were assessed by meta-analysis. The sensitivity of the PPI for 3-week survival ranged from 51 to 92% and specificity ranged from 60.0 to 94.0%, respectively. The sensitivity and specificity of the PPI for 6-week survival were from 46.0 to 89.1% and from 51.7 to 84.4%, respectively. The pooled sensitivity and specificity of the PPI for 3-week survival were 68% (6 as cutoff) and 76% (6 as cutoff), respectively. As for 6-week survival prediction,</td>
<td>Standards needed – disagree with authors’ criteria of “useful prognosticator”</td>
<td></td>
</tr>
</tbody>
</table>
the pooled sensitivity and specificity were 68% (4 as cutoff) and 82% (4 as cutoff), respectively. Conclusion: The PPI is a useful prognosticator of life expectancy of patients in palliative care, especially for patients with short survival time. However, there were no universal cutoff, and the predicted life span varies."

"Due to small number of studies and poor qualities of them, result may alter as more studies with better quality are enrolled in the future."

| 38. Montagnani et al. 2018 | liver resection in metastatic gastric cancer (GC) | 33 | 1304 | Prognostic factors identified in the literature | "Our analysis demonstrates a 5yOS rate of 22% (95%CI: 18-26%) and 10yOS rate of 11% (95%CI: 7-18%) among patients undergoing radical hepatectomy. A favorable effect on OS was shown by several factors linked to primary cancer (lower T and N stage, no lympho-vascular or serosal invasion) and burden of hepatic disease (<=3 metastases, unilobar involvement, greatest lesion<5cm, negative resection margins). Moreover, lower CEA and CA19.9 levels and post-resection chemotherapy were associated with improved OS."

Prognostic/predictive value of small set of parameters confirmed, highly specific context of condition and/or therapy |

39. Pereira et al. 2018 | Advanced cancer (metastatic disease) | 9 | 1496 | Phase angle | "Low PA was associated with worse nutrition status evaluated by body mass index, serum albumin level, transferrin, and fat-free mass. The median OS of the included papers varied from 25.5–330 days, and all studies analyzed showed a significant association between PA and OS, in that patients with low PA had worse OS. Future studies are necessary to justify the use of PA in therapeutic decisions for this population and to evaluate whether nutrition

Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed, further research recommended |

| 64 |
| 40. Pinart et al. 2018 | metastatic castration-resistant prostate cancer | 12 | 8750 | Prognostic models identified in the literature | "Models included 4-11 predictor variables, mostly hemoglobin, baseline PSA, alkaline phosphatase, performance status, and lactate dehydrogenase. Very few incorporated Gleason score. Two models included predictors related to docetaxel and mitoxantrone treatments. Model performance after internal validation showed similar discrimination power ranging from 0.62 to 0.73. Overall survival models were mainly constructed as nomograms or risk groups/score. Two models obtained an overall judgment of low risk of bias. CONCLUSIONS: Most models were not suitable for clinical use due to methodological shortcomings and lack of external validation. Further external validation and/or model updating is required to increase prognostic accuracy and clinical applicability prior to their incorporation in clinical practice as a useful tool in patient management." |

| 41. ter Veer et al. 2018 | metastatic oesophagogastric cancer | 46 | 15,392 | Prognostic and predictive factors as identified from multivariate regression analyses in study reports. Factors were considered potentially |

identified in the source studies: clinically relevant if statistically significant (\(P \leq 0.05\)) in multivariate analysis in \(\geq 50\%\) of the total number of patients in the pooled sample of the RCTs and were reported with a pooled sample size of \(\geq 600\) patients in the first-line or \(\geq 300\) patients in the beyond first-line setting. Predictive factors were identified from time-to-event stratified treatment comparisons and deemed potentially clinically relevant if the P-value for interaction between subgroups was \(\leq 0.2\) and the hazard ratio in one of the subgroups was significant (\(P \leq 0.05\)).”

“Seventeen prognostic factors for overall survival in the first-line and four in the beyond first-line treatment setting were potentially clinically relevant. Twenty-one predictive factors in first-line and nine in beyond first-line treatment setting were potentially relevant regarding treatment efficacy.”

“The prognostic and predictive factors identified in this systematic review can be used to characterise patients in clinical practice, be included in future trial designs, enrich prognostic tools and generate hypotheses to be tested in future research to promote patient-centred treatment.”

| 42. Wang C et al. 2018 | pulmonary metastasectomy in liver cancer | 17 | 513 | Prognostic factors as identified from the source studies | “The poor prognostic factors were disease-free interval (DFI) < 12 months \((HR = 2.421 \text{ 95\% CI 1.384 4.236})\) and existence of cirrhosis \((HR = 1.936 \text{ 95\% CI 1.031 3.636}).\)” | Familiar parameters validated from a large number of candidates | clinically relevant |
| 43. Wang J et al. 2018 | extracorporeal cardiopulmonary resuscitation | 16 | 1162 | Prognostic factors as identified from the source studies | The following survival predictors of ECPR were identified:  
out-of-hospital cardiac arrest (CA) (OR 0.58, 95% CI 0.36-0.93, P = .02)  
in-hospital CA (OR 1.73, 95% CI 1.08-2.77, P = .02)  
witnessed CA (OR 5.2, 95% CI 1.18-22.88, P = .01)  
bystander cardiopulmonary resuscitation (CPR) (OR 7.35, 95% CI 2.32-23.25, P < .01)  
initial shockable rhythm (OR 2.29, 95% CI 1.53-3.42, P < .01)  
1st recorded nonshockable rhythm (OR 0.44, 95% CI 0.29-0.66, P < .01)  
CPR duration (MD -13.84 minutes, 95% CI -21 to -6.69, P < .0001)  
arrest-to-extracorporeal membrane oxygenation (ECMO) (MD -17.88 minutes, 95% CI -23.59 to -12.17, P < .01)  
PH (MD 0.14, 95% CI 0.08-0.21, P < .01)  
lactate (MD -3.66 mmol/L, 95% CI -7.15 to -0.17, P = .04)  
percutaneous coronary intervention (PCI) (OR 1.63, 95% CI 1.02-2.58, P = .04). | Prognostic/predictive value confirmed (11 factors) |
<table>
<thead>
<tr>
<th>Study</th>
<th>Disease</th>
<th>Sample Size</th>
<th>Circulating biomarker</th>
<th>Predictive Value</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang et al. 2018</td>
<td>Breast cancer</td>
<td>11</td>
<td>Circulating cell-free DNA (cfDNA)</td>
<td>Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed, further research recommended</td>
<td></td>
</tr>
<tr>
<td>Zhang et al. 2018</td>
<td>Cancer</td>
<td>10</td>
<td>LINC00152, a novel long noncoding RNA (lncRNA)</td>
<td>Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed, novel factor, further research required</td>
<td></td>
</tr>
<tr>
<td>Aleksova et al. 2019</td>
<td>Heart transplantation</td>
<td>21</td>
<td>Risk prediction scores – 16 identified in the literature</td>
<td>Tools (scores, indices) – inconsistent or poor performance</td>
<td></td>
</tr>
</tbody>
</table>

“cfDNA was shown to be significantly associated with PFS (HR 2.02, 95% CI 1.51-2.72, \(P < .001\), I = 82%) and OS (HR 1.75, 95% CI 1.01-3.05, \(P < .001\), I = 92%). The results of subgroup analyses also revealed that cfDNA was a good predictor of prognosis in breast cancer patients. CONCLUSION: Our meta-analysis indicated that cfDNA was associated with poor PFS and OS, thus it may help to predict outcomes of patients with breast cancer. However, further studies are needed to confirm our results.”

“[E]levated LINC00152 could predict unfavorable OS with pooled HR of 1.66 (95% CI: 1.29-2.13, \(p=.0001\)) and poor DFS (HR=2.13, 95% CI: 1.39-3.25, \(p=.0005\)) in cancer patients. CONCLUSION: LINC00152 was correlated with advanced clinicopathological features and poor prognosis as a novel predictive biomarker in various cancers.”

“Seven (44%) scores were validated in external cohorts and 8 (50%) assessed model performance. Overall model discrimination ranged from poor to moderate (C-statistic/area under the receiver operating characteristics 0.54-0.77). The IMPACT score was the most widely validated, was well calibrated in two large registries, and was best at discriminating 3-month survival (C-statistic 0.76). Most scores did not perform particularly well in any cohort in which they were assessed. This review shows that there are insufficient data to recommend...”
the use of one model over the others for prediction of post-HT outcomes.”

<table>
<thead>
<tr>
<th>Study</th>
<th>Condition</th>
<th>n</th>
<th>Description</th>
<th>Hazard Ratio (HR) with 95% CI</th>
<th>p-value</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antoniou et al. 2019</td>
<td>Abdominal Aortic Aneurysm</td>
<td>7</td>
<td>degenerative loss of skeletal muscle</td>
<td>HR 1.66 (1.15-2.40)</td>
<td>.007</td>
<td>CONCLUSION: There is a significant link between low skeletal muscle mass and mortality in patients undergoing AAA repair. Prospective studies validating the use of body composition for risk prediction after aortic surgery are required before this tool can be used to support decision making and patient selection.”</td>
</tr>
<tr>
<td>Cao et al. 2019</td>
<td>Cervical cancer</td>
<td>19</td>
<td>pretreatment thrombocytosis</td>
<td>HR 1.50 (1.19-1.88)</td>
<td>.001</td>
<td>CONCLUSION: There is a significant link between low skeletal muscle mass and mortality in patients undergoing AAA repair. Prospective studies validating the use of body composition for risk prediction after aortic surgery are required before this tool can be used to support decision making and patient selection.”</td>
</tr>
<tr>
<td>49. Feng Q et al. 2019</td>
<td>Primary gastric cancer</td>
<td>101 model developments and 32 external validations</td>
<td>Models for predicting overall survival</td>
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<td>“The median (range) of training sample size, number of death, and number of final predictors were 360 (29 to 15320), 193 (14 to 9560), and 5 (2 to 53), respectively. Ninety-one models were developed from routine clinical data. Statistical assumptions were reported to be checked in only nine models. Most model developments (94/101) used complete-case analysis. Discrimination and calibration were not reported in 33 and 55 models, respectively. The majority of models (81/101) have never been externally validated. None of the models have been evaluated regarding clinical impact.”</td>
<td>Most models not suitable for clinical use; further validation/updating required</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>50. Feng W et al. 2019</th>
<th>patients with metastatic colorectal cancer receiving bevacizumab as first-line chemotherapy</th>
<th>7</th>
<th>1,219</th>
<th>serum lactate dehydrogenase (LDH) level</th>
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<tbody>
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<td>“Meta-analysis of all studies revealed that high serum LDH level is associated with shorter PFS (HR: 1.43, 95% CI: 1.05-1.94; P=0.023) and OS (HR: 1.667, 95% CI: 1.230-2.259; P=0.001) times in mCRC patients treated with bevacizumab-based first-line chemotherapy. However, there was no significant association between serum LDH and objective response rate. Conclusions: High serum LDH level is significantly associated with shorter PFS and OS time and may have utility as a prognostic factor for mCRC patients receiving bevacizumab as first-line chemotherapy and as a predictive Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed</td>
</tr>
</tbody>
</table>

51. Fernando et al. 2019  
in-hospital cardiac arrest  23  
Pre-arrest and intra-arrest prognostic factors  
Pre-arrest factors associated with reduced odds of survival after in-hospital cardiac arrest:  
- male sex (odds ratio 0.84, 95% confidence interval 0.73 to 0.95, moderate certainty),  
- age 60 or older (0.50, 0.40 to 0.62, low certainty),  
- active malignancy (0.57, 0.45 to 0.71, high certainty),  
- history of chronic kidney disease (0.56, 0.40 to 0.78, high certainty)  
Intra-arrest factors associated with increased odds of survival:  
- witnessed arrest (2.71, 2.17 to 3.38, high certainty),  
- monitored arrest (2.23, 1.41 to 3.52, high certainty),  
- arrest during daytime hours (1.41, 1.20 to 1.66, high certainty),  
- initial shockable rhythm (5.28, 3.78 to 7.39, high certainty).  
Intra-arrest factors associated with reduced odds of survival:  

Prognostic/predictive value confirmed (10 factors)
<table>
<thead>
<tr>
<th>Study</th>
<th>Disorder</th>
<th>n</th>
<th>Prognostic Factors</th>
<th>Prognostic/Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>52. Glasmacher et al. 2019</td>
<td>c9orf72RE disorders, including amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD)</td>
<td>206</td>
<td>prognostic factors in c9ALS, c9FTD, c9ALS-FTD, and atypical phenotypes</td>
<td>The median (95% CI) survival (in years) differed significantly between patients with c9ALS (2.8 [2.67-3.00]), c9FTD (9.0 [8.09-9.91]), and c9ALS-FTD (3.0 [2.73-3.27]); survival in atypical phenotypes varied substantially. Older age at onset was associated with shorter survival in c9ALS (HR, 1.03; 95% CI, 1.02-1.04; P &lt; .001), c9FTD (HR, 1.04; 95% CI, 1.02-1.06; P &lt; .001), and c9ALS-FTD (HR, 1.02; 95% CI, 1.004-1.04; P = .016). Bulbar onset was associated with shorter survival in c9ALS (HR, 1.64; 95% CI, 1.27-2.08; P &lt; .001). Age at onset and bulbar onset ALS remained significant in multivariable regression including variables indicating potential diagnostic ascertainment bias, selection bias, and reporting bias. Family history, sex, study continent, FTD subtype, or the presence of additional pathogenic sequence variants were not significantly associated with survival. Clinical phenotypes in patients with neuropathologically confirmed frontotemporal lobar degeneration-TDP-43, motor neuron disease-TDP-43 and frontotemporal lobar degeneration-motor neuron disease-TDP-43 were heterogenous and impacted on survival.</td>
</tr>
<tr>
<td>53. Graizel et al. 2019</td>
<td>oral squamous cell carcinoma</td>
<td>11</td>
<td>cancer-associated fibroblasts (CAFs)</td>
<td>Univariate Cox regressions showed that high CAF density was a negative prognostic factor in Single marker Cox (i.e. relative)</td>
</tr>
</tbody>
</table>
studies with female and male majority [OR 5.329 (95% CI 3.223-8.811), p < 0.001, and OR 2.208 (95% CI 1.717-2.839), p < 0.001, respectively]. High CAF density with male majority was associated with a more favorable prognosis [OR 0.996 (95% CI 0.979-1.013), p < 0.001]. Multivariate Cox regressions showed that death risk was significantly higher among patients with high CAF density compared to low CAF [OR 2.741 (95% CI 2.220-3.384) p < 0.001]. High mean age and male proportion were significantly protective [OR 0.940 (95% CI 0.925-0.955), p < 0.001, OR 0.125 (95% CI 0.018-0.867), p = 0.035), respectively].

CONCLUSIONS: CAFs increased death risk, male majority, and higher mean age were protective. A clinically validated cutoff for CAF density could serve as a reliable prognostic tool.

<table>
<thead>
<tr>
<th>Study</th>
<th>Cancer Type</th>
<th>Methodology</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>He et al. 2019</td>
<td>Colorectal cancer with surgical resection</td>
<td>Prediction models identified through various datasets</td>
<td>Models can potentially assist clinical decision-making. Besides developing new models, future research should also focus on validating existing prediction models and investigating their real-word impact and cost-effectiveness for CRC prognosis in clinical practice.</td>
<td></td>
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<tr>
<td>Jiang et al. 2019</td>
<td>Non-small cell lung cancer (NSCLC)</td>
<td>Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed</td>
<td>Randomized model analyzing multivariate Cox Proportional Hazards Regression indicated that higher abundance of CTCs significantly predicts poorer prognosis of lung cancer cases basing</td>
<td>Most models not suitable for clinical use; further validation/updating required.</td>
</tr>
<tr>
<td>Study</td>
<td>Disease</td>
<td>Sample Size</td>
<td>Marker</td>
<td>Outcome</td>
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<tr>
<td>56. Li S et al. 2019</td>
<td>Breast cancer</td>
<td>19, 12,505</td>
<td>Programmed cell death ligand-1 expression</td>
<td>PD-L1 expression was significantly associated with lymph node metastasis (P &lt; .001), high tumor grade (P &lt; .001), negative hormone receptor (P &lt; .001), human epidermal growth factor receptor 2 (HER2) positivity (P &lt; .001), high Ki67 (P &lt; .001), and high tumor-infiltrating lymphocytes (TILs) (P &lt; .001). PD-L1 expression had no significant impact on CSS (pooled HR 0.83, 95% CI = 0.64-1.09, P = .19) or MFS (pooled HR 1.11, 95% CI = 0.62-1.97, P = .72), but significantly correlated with shortened OS (pooled HR 1.52, 95% CI = 1.14-2.03, P = .004) and DFS (pooled HR 1.31, 95% CI = 1.14-1.51, P &lt; .000). Subgroup analysis showed that not PD-L1 RNA expression, but protein expression was associated with shorter survival, in addition, the adverse prognostic effect of PD-L1 expression remained in luminal A, luminal B, and HER2 subtype, not in basal-like or triple-negative subtype.</td>
</tr>
<tr>
<td>57. Li W et al. 2019</td>
<td>Brain metastasis in non-small cell lung cancer</td>
<td>18, 4373</td>
<td>Mutation of the epidermal growth factor receptor (EGFR)</td>
<td>Mutated EGFR associated with significantly improved OS compared with wild type. Subgroup analyses suggested that this relationship persisted in studies conducted in Eastern, with retrospective design, with sample size &gt;=500, mean age of patients &gt;=65.0 years,</td>
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</table>
percentage male < 50.0%, percentage of patients receiving tyrosine kinase inhibitor >=30.0%. Finally, although significant publication bias was observed using the Egger test, the results were not changed after adjustment using the trim and fill method.

CONCLUSIONS: This meta-analysis suggests that EGFR mutation is an important predictive factor linked to improved OS for NSCLC patients with brain metastases. It can serve as a useful index in the prognostic assessment of NSCLC patients with brain metastases."

| 58. Mierzynska et al. 2019 | cancer | 44 | baseline patient-reported outcomes (PROs) | "Of the 44 studies published between 2006 and 2018 that were included in our review, more standardisation and rigour of the methods used for prognostic factor analysis was found compared with the previous review. 41 (93%) of the trials reported at least one PRO domain as independently prognostic. The most common significant prognostic factors reported were physical functioning (17 [39%] studies) and global health or quality of life (15 [34%] studies). These findings highlight the value of PROs as prognostic or stratification factors in research across most types of cancer." |
| 59. Pergialiotis et al. 2019 | Ovarian cancer | 11 (5 in meta-analysis) | 1816 (856 in meta-analysis) | prechemotherapy hemoglobin (Hgb) levels | "Compared with patients with anemia, patients with Hgb levels >12 g/dL had increased odds of overall survival (odds ratio, 1.72; 95% confidence interval: 1.41, 2.10)." "Current evidence suggests that prechemotherapy Hgb levels below the threshold of 12 g/dL can potentially predict worse overall survival of OC patients. Future research is required in the field to elucidate Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed, further research recommended |

whether several independent variables such as the stage and histology of disease and rates of optimal debulking affect the clinical significance of this association.”

<table>
<thead>
<tr>
<th>No.</th>
<th>Authors et al. year</th>
<th>Disease</th>
<th>N</th>
<th>miRNAs</th>
<th>Summary</th>
</tr>
</thead>
</table>
| 60. | Rutherford et al. 2019 | colorectal cancer (CRC) | 27 | 12,544 (unclear from abstract if refers to all 27 or the 25 studies which find association with survival) | Patient-reported outcomes | In 25 of 27 studies (n = 12,544), at least one PRO was significantly associated with survival. Physical functioning, fatigue, pain and appetite loss predicted OS more often than other PROs in metastatic disease (19/27 studies). One study explored PRO predictors in early-stage CRC, finding emotional well-being and mood predicted OS. In mixed-stage samples (7/27 studies), physical functioning predicted OS more often than other PROs.”

“Physical and psychological functioning, pain, fatigue and appetite loss had prognostic significance above and beyond clinical predictors in CRC.”

| 61. | Sabarimurugan et al. 2019 | Nasopharyngeal cancer (NPC) | 21 | 5069 | miRNAs | “The forest plot was generated using cumulated survival data, resulting in a pooled HR value of 1.196 (95% CI: 0.893-1.601) indicating that the upregulated miRNAs increased the likelihood of death of NPC patients by 19%.”

 “[T]he combined effect estimate of HR across multiple studies indicated that increased miRNA expression in NPC potentially leads to poor overall survival. However, further large-scale prospective studies on the clinical significance of the miRNAs, with sizable cohorts are necessary in order to obtain conclusive results.”

|  |  |  |  |  |  | PROMS (no new information to patients) |
| |  |  |  |  |  | Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed, further research recommended |

62. Sun et al. 2019  
**Colorectal cancer**  
10  
6372  
**preoperative prognostic nutritional index (PNI)**  
"Our overall analysis indicated that the low-PNI group had a significantly reduced overall survival (OS) (HR = 1.87, 95% CI = 1.45-2.42, P < 0.01), cancer-specific survival (HR = 1.53, 95% CI = 1.07-2.19, P = 0.02), and disease-free survival (HR = 1.67, 95% CI = 1.23-2.26, P < 0.01) compared with the high-PNI group. Furthermore, our subgroup results indicated that a high PNI could be a significant indicator of improved OS in TNM stage II (HR = 1.93, 95% CI = 1.29-2.90, P < 0.01) and III (HR = 1.71, 95% CI = 1.25-2.34, P < 0.01), and a similar trend in TNM stage I or IV could also be observed though without statistical significance. Regarding postoperative complications, our pooled results indicated that the low-PNI group had a significantly increased incidence of total and severe postoperative complications. **CONCLUSIONS:** Our findings indicated that CRC patients with a preoperative high PNI had a significantly improved OS. However, almost only Asian CRC patients were included based on current issue."

63. Wang M et al. 2019  
**cancer**  
6  
1584  
**TRIM59**  
"The results showed that high levels of TRIM59 were significantly associated with poor OS in cancer patients (HR = 1.43, 95%CI: 1.24-1.66, P < .001), indicating that higher TRIM59 expression could be an independent prognostic factor for poor survival in cancer patients. **CONCLUSION:** Our meta-analysis suggests that higher TRIM59 expression predicts poor prognosis in cancer patients, and it may therefore serve as a promising prognostic factor."

<table>
<thead>
<tr>
<th>No.</th>
<th>Authors</th>
<th>Study Type</th>
<th>Sample Size</th>
<th>Prognostic Factors</th>
<th>Prognostic/Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>64.</td>
<td>Wang SJ et al., 2019</td>
<td>Repeat hepatectomy for recurrent colorectal liver metastasis (CRLM)</td>
<td>34, 3039</td>
<td>Prognostic factors as identified in the literature</td>
<td>Pooled analysis showed that primary T3/T4 stage tumor (HR = 1.94; 95% CI: 1.04-3.63), multiple tumors (HR = 1.49; 95% CI: 1.10-2.01), largest liver lesion &gt;=5cm (HR = 1.89; 95% CI: 1.11-3.23) and positive surgical margin (HR = 1.80; 95% CI: 1.09-2.97) at initial hepatectomy, and high serum level of carcinoembryonic antigen (HR = 1.87; 95% CI: 1.27-2.74), disease-free interval &lt;=12 months (HR = 1.34; 95% CI: 1.10-1.62), multiple tumors (HR = 1.64; 95% CI: 1.32-2.02), largest liver lesion &gt;=5cm (HR = 1.85; 95% CI: 1.34-2.56), positive surgical margin (HR = 2.25; 95% CI: 1.39-3.65), presence of bilobar disease (HR = 1.62; 95% CI: 1.19-2.20), and extrahepatic metastases (HR = 1.60; 95% CI: 1.23-2.09) at repeat hepatectomy were significantly associated with poor OS. CONCLUSIONS: Repeat hepatectomy is a safe and effective therapy for recurrent CRLM. Long-term outcome is predicted mainly by factors related to repeat hepatectomy.</td>
</tr>
<tr>
<td>65.</td>
<td>Wang X and Wang Y, 2019</td>
<td>Gynaecological cancer</td>
<td>9, 2373</td>
<td>Prognostic nutritional index (PNI)</td>
<td>The PNI correlated closely with the OS and PFS of gynaecological cancer; the pooled HRs were respectively 2.66 (95% CI 1.56-4.55) and 2.43 (95% CI 2.07-2.86) on univariate analysis (UVA) and 1.88 (95% CI 1.10-3.20) and 1.92 (95% CI 1.52-2.44) on multivariate analysis (MVA). Conclusions: The PNI is significantly associated with the prognosis of patients with gynaecological cancer, and may, in fact, be independently prognostic.</td>
</tr>
<tr>
<td>66.</td>
<td>Yang C et al., 2019</td>
<td>Patients with malignant solid tumors</td>
<td>17, 2,228</td>
<td>T-cell lymphoma invasion and</td>
<td>The overall estimated results showed that high Tiam1 expression was significantly associated with shorter overall survival (HR=2.08, 95% CI:</td>
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</table>


Petrova M. et al. BMJ Support Palliat Care 2022;0:1–15. doi: 10.1136/bmjspcare-2021-003066
<table>
<thead>
<tr>
<th>Study Ref</th>
<th>Study Type</th>
<th>N</th>
<th>Prevalence (%)</th>
<th>Data Summary</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>67. Yang L et al. 2019</td>
<td>Nasopharyngeal carcinoma (NPC)</td>
<td>21</td>
<td>2921</td>
<td>High/positive expression of ERCC1 predicted poor objective response rate (ORR) (OR = 2.83; 95% CI = 2.11-3.80; P &lt;.001), overall survival (OS) (HR = 1.77; 95% CI = 1.48-2.12; P &lt;.001), and disease-free survival (DFS) (HR = 1.60; 95% CI = 1.43-1.79; P &lt;.001) in NPC. Low heterogeneity was detected among these studies (ORR: I = 0.0%, P = .776; DFS: I = 38.7%, P = .148; OS: I = 0.0%; P = .530). The results of sensitivity analyses and publication bias verified the reliability of our findings. CONCLUSIONS: This study suggested ERCC1 as a potential predictive and prognostic biomarker for the treatment response and survival prognosis of NPC patients.”</td>
<td>Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed</td>
</tr>
<tr>
<td>68. Yang M et al. 2019</td>
<td>Lung cancer</td>
<td>13</td>
<td>1,810</td>
<td>The pooled prevalence of sarcopenia was 43% in patients with non-small cell lung cancer (NSCLC) and 52% in patients with small cell lung cancer (SCLC). Sarcopenia was associated with unclear), prognostic/predictive value confirmed</td>
<td>Single marker (i.e. relative importance unclear),</td>
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</table>
A shorter overall survival (OS) in patients with lung cancer (hazard ratio [HR], 2.23; 95% CI, 1.68-2.94). This association existed for both NSCLC (HR, 2.57; 95% CI, 1.79-3.68) and SCLC (HR, 1.59; 95% CI, 1.17-2.14). Sarcopenia was an independent predictor of shorter OS in both stage I-II NSCLC (HR, 3.23; 95% CI, 1.68-6.23) and stage III-IV NSCLC (HR, 2.19; 95% CI, 1.14-4.24). However, sarcopenia was not an independent predictor of disease-free survival in patients with NSCLC (HR, 1.28; 95% CI, 0.44-3.69). Conclusions: Sarcopenia is highly prevalent in patients with lung cancer (approximately one in two) and an important predictor of impaired OS in patients with SCLC or with different stages of NSCLC.

| 69. Yu et al. 2019 | Liver failure | 13 | 2071 | hepatic encephalopathy | "The results proved the prognostic value of hepatic encephalopathy for survival of patients with liver failure (OR=5.62, 95%CI=6.30-9.82, P<0.001). The subgroup analyses showed that the type of liver failure and the follow up duration may be the factor influencing the association between hepatic encephalopathy and survival of patients with liver failure." | Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed |
| 70. Cao et al. 2020 | Gastric cancer | 28 | 15,617 | platelet-to-lymphocyte ratio (PLR) | "The pooled results indicated that elevated PLR was associated with poor OS (HR: 1.37; 95% CI: 1.24-1.51; P < 0.001). A significant publication bias was observed (Egger test, P = 0.036; Begg test, P = 0.017). After adjusting for publication bias using the trim and fill method, an adjusted pooled HR of 1.19 (95% CI: 1.08-1.33; P = 0.001) was observed. Subgroup analyses indicated an elevated PLR in retrospective studies. Studies conducted in Turkey, the UK, the USA, and Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed, limitations of included studies (i.e. further |
Costa Rica; studies with a sample size of < 1000, with < 70% male patients, and with patients treated with chemotherapy; studies with PLR cutoff value of >=200; and studies with lower quality as determined by the Newcastle-Ottawa Scale all showed greater harmful effects on OS than their corresponding subsets (P < 0.05).

CONCLUSIONS: An elevated PLR was associated with poor OS in patients with gastric cancer. These results might differ between studies due to differences in design, country of origin, sample size, sex proportion, treatment strategy, PLR cutoff value, and study quality.

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71. Zhao et al. 2020

**gastric cancer**

<table>
<thead>
<tr>
<th>Research</th>
<th>13</th>
<th>7004</th>
<th>Perineural invasion</th>
</tr>
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</table>

"There were significant relationships between PNI and a series of unfavourable clinicopathological factors including undifferentiated histology type (OR: 1.78, 95% CI 1.37 to 2.33, p<0.001; I<sup>2</sup>=75.3%), diffuse type (OR: 1.96, 95% CI 1.07 to 3.60, p=0.029; I<sup>2</sup>=79.5%), lymphatic invasion (OR: 7.00, 95% CI 3.76 to 13.03, p<0.001; I<sup>2</sup>=83.6%), vascular invasion (OR: 5.79, 95% CI 1.59 to 21.13, p=0.008; I<sup>2</sup>=95.8%), deeper tumour invasion (OR: 4.79, 95% CI 3.65 to 6.28, p<0.001; I<sup>2</sup>=65.0%) and lymph node metastasis (OR: 3.60, 95% CI 2.37 to 5.47, p<0.001; I<sup>2</sup>=89.6%). In addition, PNI was significantly associated with worse survival outcome in GC patients (HR: 1.69, 95% CI 1.38 to 2.06, p<0.001; I<sup>2</sup>=71.0%)."

Single marker (i.e. relative importance unclear), prognostic/predictive value confirmed.