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Diabetes and Palliative Care: A Framework to Help Clinicians Proactively Plan for Personalized care

Trisha Dunning and Peter Martin

Abstract

The aim of the chapter is to provide a brief overview of diabetes and the associated morbidities that affect life expectancy to highlight why proactively planning for palliative and end-of-life care is essential to quality personalized diabetes care. Life expectancy may not be significantly reduced if blood glucose, lipids and blood pressure are well controlled; but several diabetes-related complications and long duration of diabetes affect life expectancy. Significantly, complications and related organ and tissue damage can be present 10–15 years before type 2 diabetes is diagnosed. The challenge of prognostication is discussed as recommendations for when to consider changing the focus of care from preventing diabetes complications to palliation and comfort care. Life-limiting illness and palliative and end-of-life care are defined. A framework for integrating diabetes and palliative care is proposed. The framework could help clinicians and people with diabetes prevent/manage complications and plan care to maintain quality of life, dignity and autonomy and ameliorate suffering as their life trajectory changes. The framework aims to facilitate care transitions and help clinicians proactively initiate management and have timely meaningful conversations about palliative and end-of-life care with older people with diabetes and their families.

Keywords: diabetes, complications, comorbidity, life-limiting illness, palliative, end of life, diabetes palliative care framework

1. Introduction

Diabetes is the most common chronic disease. People are at risk of diabetes due to genetic inheritance, epigenetic factors, age and lifestyle-related factors. The International Diabetes Federation (IDF) [1] estimated 123 million people aged 65–99 had diagnosed diabetes and predicted the number would increase to 438 million by 2045. Most older people have type 2 diabetes (T2DM), but people with type 1 diabetes (T1D) survive to older age. These data do not take account of the people with prediabetes who may already have one or more life-limiting diabetes complications at diagnosis.

An estimated ~ 20 million people globally need palliative care the year before they die; a further 20 million need end-of-life care per year [2]. The World Health Organization (WHO) estimated that 71% of deaths in 2016 were associated

with diabetes complications. Most (~67%) occur in people aged 60 and older [3]. Therefore, older people with diabetes may have more than one life-limiting condition.

Aging is associated with reduced insulin production and insulin sensitivity that lead to insulin resistance, which increases by 1–2% per year [4]. Older age is generally defined as older than age 65 [5]. However, chronological age is not a good guide to disease, functional status, care needs or life expectancy. Biological age is a more accurate indicator of the rate at which body cells deteriorate but is more difficult to measure. Significantly, the individual's chronological and biological age may be different [5].

Many older people have several coexisting comorbidities/geriatric syndromes, including cardiovascular disease, renal disease, sensory impairments, lower limb pathology, cognitive changes/dementia, some forms of cancer and frailty that individually and collectively affect life expectancy [6–9]. Frailty predicts admission to a care home and mortality and increases the risk of death [10, 11]. Frailty is assessed in various ways, including phenotype and accumulation of deficits. The latter may be more useful to prognostication.

Many older people with diabetes have at least three coexisting comorbidities, but these are often managed as single entities that may not address the many diffuse symptoms [12–14] or the need to change the focus of care from achieving normoglycaemia to prevent complications to focus on comfort by managing existing complications and preventing hypoglycaemia and hyperglycaemia.

People with diabetes who can maintain near-normal glycaemia (~7%) and normal lipids and blood pressure are less likely to develop complications and may not have significantly reduced life expectancy. However, these parameters are often abnormal some 10–15 years before type 2 diabetes (T2DM) is diagnosed, and complications can be present and affect life expectancy from diagnosis [7, 12]. In addition, older people are less likely to benefit and more likely to be harmed by 'tight blood glucose control'. Therefore, blood glucose and HbA1c target ranges need to be individualized to minimize risk, especially hypoglycaemia risk and other risk factors being managed [15, 16].

Diabetes and the associated comorbidities affect the quality of life, compromise function and self-care and increase the need for hospital admissions and readmissions and eventually lead to death [11, 13, 17]. Over 50% of people aged 65–80 experience moderate to severe disability and increased dependency. On average, they need care 24 hours/day between 1.3 and 6.9 years [18].

Significantly, older people with diabetes and concomitant heart failure who have several recent hospital admissions and consult multiple prescribers are at risk of readmission within 30 days [19]. Hospital admissions near the end of life often result in burdensome and futile treatment that causes significant suffering and stress for the individual and their family [19, 20]. Likewise, people with cognitive impairment face many challenges, including decisions about their care.

Thus, starting conversations about the likely prognosis early in the disease trajectory can enhance people's capacity to make meaningful decisions and enable them to document their values and care preferences [21, 22]. In turn, clearly documented values and care preferences enhance family and health professionals' capacity to make care decisions consistent with the person's values and reduce decisional uncertainty.

2. Diabetes care

Quality diabetes care is described in many clinical guidelines such as the IDF [7], American Association of Diabetes/European Association for the Study of

Diabetes [23], Australian Diabetes Society [24] and Diabetes UK [25]. Many recommend 'relaxing' glycaemic targets in older people to reduce the risk of hypoglycaemia and its consequences: they usually do not include *comprehensive* guidance about other key aspects of palliative and end-of-life care. Exceptions are the IDF Global Guideline for Managing Older People with T2DM [7] and Guidelines for Managing Diabetes at the End of Life (currently under review) [8] and Diabetes UK [26].

Quality diabetes care encompasses achieving normoglycaemia (HbA1c <6.5 7%), controlling blood lipids and blood pressure using diet and exercise and commencing glucose-lowering (GLM), lipid-lowering and antihypertensive agents and other medicines when indicated, providing diabetes self-care education and undertaking regular health assessments. Self-care and adherence to recommendations are important to maintain health and meet metabolic targets.

Assessments could also encompass determining when the individual could benefit from palliative care and when to document an end-of-life care plan and an advance care directive (ACD). However, many clinicians find it difficult to discuss death and dying (giving bad news). Consequently, they miss opportunities to initiate conversations about these issues, and beneficial palliative care can be delayed [20, 21, 27]. Death cannot be cured: people's end-of-life can be made comfortable, dignified and consistent with their values and care preferences when these are known, clearly documented and communicated.

Many clinicians regard death and dying as treatment failure [28]. The terms 'failure' and 'bad news' are inherently negative. People often know they are not going to recover and want affirmation from their health professionals [28]. Some people express the wish to die while their identity and personhood can be maintained and not when they are terminally ill and incapable of making rational thoughts and informed decisions [29]. When such discussion does occur, health professionals often present the options as a choice between continuing and withdrawing treatment.

3. Palliative care

Palliative care originated in the 1960s and largely focused on end-of-life care at that time. More recently, there is increasing recognition that people with chronic disease could benefit from palliative care; thus the term broadened in meaning and scope to include non-communicable chronic diseases [30]. Most adults with chronic disease need palliative care as a result of cardiovascular disease [9, 11]. Diabetes is the leading cause of cardiovascular disease, and, in turn, cardiovascular disease is the leading underlying cause of diabetes-related deaths [3, 6, 31]. All health professionals who care for people with diabetes have a role in timely implementation of palliative care. Therefore, health services need to integrate such care into the services they offer and policies [32].

The patterns of dying are changing as more people follow the chronic disease trajectory, which is characterized by periods of deterioration followed by recovery until physiological reserves are depleted and the person reaches the terminal and end-of-life stages [32–34]. Many experts recommend palliative care should be implemented early in the disease trajectory, sometimes from diagnosis, for greatest benefit [30, 32]. In fact, Murray et al. recommend '[clinicians] should routinely and systematically consider whether our patients might benefit from early palliative care' [34]. **Table 1** explains the terms palliative care, life-limiting illness, end-of-life care and advance care planning.

Term	Explanation	Considerations
Life-limiting illness	<p>The term life-limiting illness (LLI) describes people at high risk of dying in the subsequent 12 months. Many people admitted to hospitals and ICUs have a life-limiting illness. The Gold Standards Framework Proactive Indicator [33] outlines indicators of life-limiting illnesses for cancer, chronic obstructive pulmonary disease, heart failure, renal disease, neurological diseases, frailty, dementia and stroke</p> <p>Diabetes is not specifically mentioned in the GSF. It does mention organ failure, kidney disease, dementia and multimorbidity. Diabetes is the main underlying cause of renal disease, cardiovascular disease and some forms of cancer, frailty and dementia. Therefore, it is often unclear what 'initial' disease commenced the underlying pathological changes, which could be an inflammatory process related to obesity</p>	<p>Diabetes experts recommend normalizing blood glucose, lipids and blood pressure to reduce the risk of complications that can reduce life expectancy</p> <p>Palliative care experts and many geriatricians recommend people to document their values and end-of-life preferences while they are able to make informed, autonomous decisions</p> <p>Fewer than 50% of people with life-limiting illnesses actually have documented goals of care, and < 24% has documented care goals [36]</p>
Palliative care	<p>The aim of palliative care is to improve the quality of life, relieve suffering and manage distressing symptoms</p> <p>Palliative care involves symptom management, prognostication, advance care planning and transition to the dying/terminal stage [36]</p> <p>Palliative care can be used at any time and can complement usual diabetes care. Palliative care should be commenced early for maximum benefit to archive these aims [3, 31]. Early palliative care also increases satisfaction with care [34]</p>	<p>Many older people with diabetes could benefit from combining palliative care into their usual diabetes care as function changes and the burden of medicines and complications increase</p> <p>They also benefit from the support to document advance care directives much earlier than it currently occurs [36, 37]</p> <p>Good communication is essential to support older people to make informed decisions and to document their values and care preferences and goals</p>
End-of-life care	<p>The last 12 months of life and includes imminent death in a few hours or days [2, 30, 33]</p> <p>Four phases are described: stable, unstable, deteriorating, terminal [38]</p>	<p>Many people want to die at home, but most older people with multiple comorbidities die in hospital [39]</p> <p>Recognize/diagnose dying</p> <p>Identify whether unstable disease is likely to be remediable or likely to continue to deteriorate and progress to the terminal stage</p> <p>Treat or implement end-of-life care</p>
Advance care directive (ACD)	<p>Advance care planning (ACP) is the process used to develop and ACD</p> <p>ACD is a document that clearly describes an individual's values and the type of treatment they want if they are not capable of deciding for themselves and guides their medical treatment decision-maker and clinicians to make decision on their behalf that accord with their values and care preference [40]</p> <p>ACDs are often first documented when the individual has a rapid response team (RRT) call to assess sudden deterioration [41, 42]</p> <p>It is important to consider cultural and religious conventions when discussing ACDs. These differ among cultures and within cultures and influence laws and regulations and the way individual's view end of life and ACDs</p>	<p>Important information for older people with diabetes to document in their ACD are the things they value and give meaning and purpose to their life (values directive), the care they <i>want</i> to receive and the care they <i>do not want</i> to receive [40]. Generally the ACD does not have to be completed all at once. Older people need time to think about the issue and discuss them with relevant people. So, start the conversation and follow up at a later time</p> <p>It is important to check the persons' care preferences as part of ongoing care because they can change over time. Values remain relatively constant</p>

Table 1.
Explanation of the terms life-limiting illness, palliative care, end-of-life care and advance care directives.

4. Diagnostic uncertainty and prognostic challenges: Challenges to discussing palliative and end-of-life care

It is certain that everybody will die eventually. The uncertainty lies in when and how an individual will die. The trajectory to death for people with diabetes can be a long and healthy one but is often a long process of physical and social decline followed by recovery until the final stages of life: the so-called chronic disease trajectory [2, 43, 44]. People can die, seemingly suddenly, during a disease exacerbation. However, most of these people have one or more indicators of limited life expectancy. Thus, their death was *possibly* predictable: the time of death might not have been. Episodes of deterioration become increasingly frequent over time and reduce the remaining physiological reserve and the person's ability to recover from subsequent exacerbations.

The chronic disease trajectory to end of life is unpredictable and includes many periods of deterioration and recovery before death occurs [38, 43, 44], which creates a degree of diagnostic uncertainty for many health professionals, people with diabetes and families. The uncertainty is compounded by challenges associated with prognostication and, sometimes, from misinterpreting individual's questions such as 'how long have I got Doc?' Mostly the individual wants an idea about how long they have left 'to put their house in order' and 'say my goodbyes'. Such questions could be a cue to health professionals to begin advance care planning to document the individual's values and care goals and preferences. Some strategies to enhance such conversations are shown in **Table 2**.

Diagnostic uncertainty encompasses cognitive, emotional and ethical reactions, which are affected by the need to discuss care options with the individual

-
- Use a value-based approach rather than focusing on medical decisions
 - Conversations can be planned or opportunistic
 - If planned ask the individual who they would like to be present during the conversation and have all relevant information and documents ready
 - Ensure the environment is confidential and welcoming
 - Ensure the person brings any communication aids they need with them, e.g. spectacles and hearing aids
 - Present the information in easy-to-understand words and formats, and assess their understanding
 - Frame the conversation as part of the individual's life story. Use own knowledge of life expectancy in similar conditions
 - Recognize and respond to verbal, non-verbal and emotional cues appropriately
Some useful questions include the following: these questions should *not be used as a 'tick box' list*. They must be personalized to the individual and the situation. The questions need not be asked in any particular order
 - What do I need to know about you to help me give you the best possible care and advice?
 - What things make your life worth living or matter to you? Rather than asking about the quality of life.
 - What does suffering mean to you?
 - What does a good death mean to you?
Not interrupting the individual is a key skill
Older people need time to process the question in order to respond—a complex cognitive process, especially when the topic is emotive. Interrupting can cause confusion and change the discussion, and important issues might not be identified
Understand and accept that not everybody is capable of making informed decisions during a crisis and some people prefer certainty, i.e. to be 'told what to do'
-

Table 2.
Strategies to enhance conversations about palliative and end-of-life care among older people with diabetes, families and clinicians [40, 49, 64, 65].

and often their families as well as organizational culture and personal experience [31] and individual tolerance of uncertainty [45]. Some degree of uncertainty occurs in nearly every aspect of health care and influence clinician and patient outcomes. Types of uncertainty include disease, therapeutic (risk and benefit) and prognosis [46].

Informed shared decision-making requires the individual to understand their illness, their treatment options and prognosis. Clinicians may not be comfortable disclosing their uncertainty to the individual [22, 46] and may refer them for a second opinion, admit them to hospital and/or order a barrage of diagnostic investigations [47]. These actions may or may not be indicated/warranted.

Sudden, unexpected death occurs in ~ 25% of deaths [2, 20]; however, diabetes-related deaths are often multifactorial, which makes it more difficult to predict life expectancy. A number of changes and well-defined patterns accompany functional decline to the end of life. These patterns are described in a series of disease trajectories [43, 44]. Prognostic indicators, include the Gold Standards Framework Proactive Identification Guidance (PIG) [35], life expectancy and risk calculators, the Diabetes Complications Severity Index (DCSI) [47], Cardiovascular risk tools and life expectancy calculators. These tools and calculators can help health professionals tailor care with the individual and start conversations about advance care planning.

Some experts recommend using absolute risk to decide which people are most likely to benefit from treatment because it considers the whole person and their individual determinates of risk [48]. These tools do not predict death. They are a guide to self-care education and care planning.

General indicators described in the GSF that indicate palliative care could be beneficial include:

- Decline in health and function.
- Unplanned hospital admissions.
- Symptoms that are difficult to manage.
- The person becomes less responsive to treatment.
- Person chooses not to accept active treatment.
- > 10 Kg progressive weight loss in the preceding 6 months.
- Serum albumin <25 g/L—other guidance suggests <5% in people with sarcopenia.
- More than 50% have a significant life event such as a fall, admission to a care home or bereavement.

In addition, a range of diabetes-related factors associated with reduced life were identified in a targeted literature review [49–51] and include:

- Long duration of diabetes.
- Macro- and microvascular complications [49]. Diabetes significantly increases the risk of all-cause and cardiovascular mortality in men and women by two- to fourfold [50].

- Glucose variability (fluctuation between high and low blood glucose levels) and rapid reduction in HbA1c [52–54].
- Multimorbidity: 80% of people 80 years and older have an average of 3.6 morbidities [54, 55].
- Severe hypoglycaemia [56–58] especially in older people and those on sulphonylureas or insulin and those with hypoglycaemic unawareness, including dementia.
- Lower limb and foot disease [59, 60].
- Polypharmacy [61].
- Cancer contributes to increased mortality in T2DM.
- Comorbid depression [62]: it is important to recognize and explore suicide ideation; suicide is twice as common in older people, and depressive symptoms are present in 80% of people > aged 74 who commit suicide. The severity of depression is a determinant of suicidal ideation [63].

This information and other prognostic indicators can be used independently or together to *guide* discussions with people with diabetes about advance care planning, their ACD and when to initiate palliative care. Documenting and ACD are part of holistic, evidence-based quality care.

4.1 Strategies that clinicians use to reduce prognostic uncertainty

Uncertainty occurs in all areas of health care, not just palliative and end-of-life care. A number of strategies can help clinicians reduce decisional uncertainty. These include:

- Acknowledging their uncertainty to themselves, colleagues, the individual and their family [46]. Not acknowledging uncertainty leads to further uncertainty and other problems. Acknowledging it can help build rapport and trust with the individual and their family.
- Accepting that death is normal and being able to recognize common disease patterns and their consequences that compromise life expectancy, signs of deterioration and signs that death is approaching. Guidance concerning these issues is described in the GSF [33], Murtagh et al. [31] and a suite of three tailored versions of information for older people with diabetes, family carers and clinicians [64].
- Understanding that many people choose comfort and quality of life over a longer life.
- Being able to recognize deterioration beyond the clinical parameters used in acute care. For example, using the GSF, which recommends asking the ‘surprise question’: ‘would I be surprised if this person died soon?’ The answer, yes or no, can guide treatment decisions, including whether and when to implement palliative care and aspects of usual diabetes care such as HbA1c, blood glucose monitoring and other metabolic parameters and when to initiate conversations about advance care planning with the individual older person and relevant others.

- Developing communication skills and the confidence to discuss palliative and end-of-life care. These skills increase following communication skills training [65] and include asking ‘good/appropriate’ questions, listening to the answers and using relevant probing and clarifying questions when relevant; see **Table 2**.
- Understanding that ACP is an iterative process that can be achieved using structured ACP communication tools and processes.
- Consulting the individual’s ACD. ACDs are an outcome of advance care planning; they inform clinicians and families about the individual’s values and preferences and enable medical treatment decision-makers, family and clinicians to make decisions consistent with the person’s values when they are unable to decide for themselves [40, 64, 65].
- Asking about subjective life expectancy such as will to live is a strong predictor of survival in all age groups and genders [66, 67].
- Asking questions about self-rated *future* health, e.g. in 5 years, and adjusting for known mortality risk factors [67].
- Considering the health and care burden of informal/family carers: their subjective care burden is linked to various health outcomes for the care recipient including mortality risk [67, 68].
- Considering relevant policies, regulations and legislation that apply where the clinician works [51, 66].

These strategies show that subjective information and shared decision-making is an important part of the health assessment and risk calculations. After all, death is a very personal experience. They can help clinicians can include palliative and end-of-life care in usual diabetes clinical practice guidelines, is important.

4.2 Some key diabetes palliative care issues

Figure 1 depicts a framework for integrating diabetes and palliative and end-of-life care based on function and the chronic disease trajectory. The information can be used as a basis for developing a personalized care plan and with usual diabetes and palliative care guidelines.

Commencing palliative care does not mean usual diabetes care is abandoned. All care must be based on the best evidence. Care must be personalized and, ideally, developed in consultation with the older individual and often their family carers. People with diabetes do receive ‘usual’ palliative care, but it may not encompass important diabetes-specific issues that need to be considered. Specific information about these issues can be found in Dunning et al. [8] and Diabetes UK [26].

4.3 Managing glycaemia

Preventing hyperglycaemia is important to prevent ketoacidosis and hyperosmolar states, both of which cause considerable discomfort and can be fatal. Likewise, preventing hypoglycaemia is imperative. It is often missed because of the changed

Framework for implementing diabetes palliative and end of life care to support function and personalised proactive care planning.

Diabetes trajectory

Basically well and functionally independent
 Consider number of comorbidities
 Functional assessment, including diabetes-self care
 Hypoglycemia risk assessment
 Medicine-related adverse event risk

Declining function in one or more:
 Comorbidities
 Polypharmacy
 Foot leg ulcers
 Severe hypoglycaemia
 Depression, social isolation
 Frailty
 Falls
 Cognitive changes or dementia
 Social isolation
 Carer burden – a predictor of the care recipient admission to a care home Discuss stopping activities such as driving when applicable

Significant functional deficits
 Sarcopenia, frailty
 Falls
 Frequent admission to hospital or Emergency department
 Declining will to live
 Self-rated future health
 Carer not able to cope

Management focus and care planning

Usual diabetes management but consider whether HbA1c and blood glucose target ranges are safe.
 Preventative care: health screening e.g. for cancer, vaccinations and dental checks. Treat reversible inter-current illness including hospital admission if needed.
 Medicine review, diet review and tailor sick day and hypo care plans to individual risk.
 Palliative care could be implemented with usual diabetes care e.g. to manage pain.

Continue complication assessments and consider referring for palliative/geriatric assessment. Treat reversible inter-current illness including hospital admission if needed, (LMOT) but there may be some treatment limitations
 Assess frailty status before surgery and before and after hospitalisation
 Revise HbA1c and other target ranges to avoid hypo and hyperglycaemia.
 Consider discussing values and care goals and use them to inform the care plan. If the person elects to develop their ACD, regularly review it to make sure their preferences have not changed. ACD should be documented before admission to a care home.
 May need protein and other supplements if malnourished and losing weight.

Palliative care/geriatric assessment and review ACD
 Medicine review may continue insulin in T1DM, Consider stopping GLMs and commencing insulin in T2DM if indicated
 Check that ACD still reflects the individuals care goals.
 Offer dignity therapy if available

Terminal Stage

End of life and terminal care
 Decide care according to the individual's values
 Simplify medicine regimen and stop most medicines
 Provide comfort care
 Implement the individual's ACD
 Pronounce death compassionately.
 Support family carers – e.g. offer bereavement counselling

Figure 1. Proposed framework for integrating diabetes care with palliative care that supports function and proactive care planning. Reproduced from Dunning et al. [72] with permission. The framework has not been formally evaluated at this stage.

symptomatology and can become chronic. Hypoglycaemia is a risk factor for frailty [69] and cardiovascular disease [70] and leads to short-term cognitive changes and dementia in the longer term.

T2DM is associated with brain aging and cognitive changes that affect memory and learning and contribute to depression in the longer term. Thus, blood glucose monitoring in a suitable regimen tailored to the medicine regimen and hypo-hyperglycaemia risk profile can provide important information about glucose variability, the medicine regimen and care needs.

4.4 Managing medicines: Pharmacovigilance

Pharmacovigilance is important and includes regular medicine reviews, stopping medicines and using non-medicine options where possible and selecting the lowest effective dose when medicines are indicated. Insulin might be a safer option than some other glucose-lowering medicines and can be used with a palliative intent, that is, to improve comfort by managing unpleasant symptoms associated with hyperglycaemia. Some medicines are diabetogenic, and it is important to diagnose hyperglycaemia caused by medicines such as glucocorticoids and manage it appropriately.

4.5 Nutrition and hydration

Undernutrition can contribute to frailty, hypoglycaemia, slow wound healing and falls and can be present in overweight individuals. Eating disorders, depression, difficulty swallowing and other causes can be present. Likewise cancer, thyroid disease and other diseases can cause weight changes. These factors highlight the value of comprehensive geriatric assessments and collaborative interdisciplinary care.

4.6 Family carers

Family carers play a vital role in the care of children and older people with diabetes by helping with diabetes self-care and other activities of daily living. They are at risk of sleep deprivation, reduced immunity, depression and unresolved bereavement after their relative dies [68]. It is important to monitor their health and provide counseling and support.

5. Summary

Long-standing diabetes and associated complications significantly increase the risk of disability and frailty and reduce life expectancy. Palliative care can be used with usual diabetes care. Proactively planning for diabetes palliative care is important. Diabetes reduces life expectancy and can cause significant suffering. Considering the indicators of reducing life expectancy and implementing palliative care early into the diabetes care plan has many benefits, including reducing the suffering and the burden on the individual and family carers. Atypical symptoms associated with older age can make it difficult to recognize deterioration and underlying causes.

People admitted to hospital near their end of life are more likely to receive burdensome treatment such as admission to intensive care, resuscitation, dialysis and blood transfusions that are often futile [45, 46] and distressing for the individual and their families. Health professionals have an important role in helping older people with diabetes to plan for predictable changes in health status and to initiate timely palliative and EOL care to prevent unnecessary admissions to hospital and/or

invasive intensive care that have little benefit, even when it prolongs life, and may not accord with the individual's core values. It is difficult for health professionals and family to make care decisions when the individual's values and wishes are not known, documented and communicated.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Author contribution

The authors conceived and wrote the chapter.

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