Predicting and communicating prognosis in palliative care

Prognostic tools can help, but should not be applied blindly

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RESEARCH, p 459

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When Abdelbaset Ali al-Megrahi, convicted of the Lockerbie bombing, was released from a Scottish prison in August 2009, he was freed on compassionate grounds. His doctors pronounced that he was terminally ill with prostate cancer and thought he had only a few months to live. He is still alive today (at the time the *BMJ* went to press). How al-Megrahi's prognosis was formulated is not known, but its accuracy may have been improved if his doctors had had access to a tool like the one developed in the linked study by Gwilliam and colleagues.[1]

Diagnosis, prognosis, and therapeutics are the three essential clinical skills and prognosis is the least well done. Doctors are rarely trained in formulating prognoses, and nor do they like doing it, so they try to avoid it.[2] But in the 21st century much of clinical practice involves caring for patients with advanced, progressive, life limiting illness. Prognosis needs to be restored as a core clinical skill, to optimise the patient's treatment and planning.

A new science of prognosis is emerging in palliative care. There are two components to the skill of prognosis—formulating the prediction and communicating it to the patient. Formulation of the prediction may be based on personal clinical judgment or an actuarial one, whereby the human element is eliminated and the prediction rests solely on statistics.[3] Some guidance is available for clinicians who wish to formulate the prognosis in their heads. It can be formulated as a temporal prediction (expressed as a date or in units of time) or a probabilistic one (expressed as the percentage chance of reaching a certain time point). So called death trajectories have been described[4]; the pattern of decline seen in terminal cancer is monophasic and easier to anticipate than for other end stage diseases.[5] Patient related factors such as performance status, symptoms, and laboratory parameters are more predictive of imminent death from cancer than are tumour related factors such as grade, stage, or genetic signatures.[6]

Temporal predictions based on clinical judgment are notoriously inaccurate and usually overoptimistic.[7] Although probabilistic predictions are more accurate, approaching that of other clinical predictions,[8] actuarial judgment of survival is now recommended.[9] Several statistical models that predict survival have been developed over the past 25 years,[10] but none has entered routine clinical practice. Most came from single institutions, had small sample sizes, evaluated limited panels of variables, and were never validated. They have rarely been compared head to head with clinical judgment.

Gwilliam and colleagues' study overcomes many of these methodological deficiencies. From a list of 80 demographic, clinical, and biochemical variables sampled in more than 1000 patients from 18 different palliative care programmes across the United Kingdom, the authors identified the 23 parameters that are independently associated with a poor prognosis. When combined in mathematical models, these variables can clearly discriminate three different prognostic subgroups that have median survivals of about one week, one month, and three months. The models have been developed with and without blood tests, so that they can be adapted to a range of palliative care situations. They are well calibrated, and correctly predict whether the patient will live for days, weeks, or months about 60% of the time. They have been internally validated via robust statistical techniques, and they performed as well as human judges, if not better. External validation is now needed, both in other palliative care populations and in patients with advanced cancer who have not yet been referred to a palliative care service.[11]

On the down side, the authors admit that their models are arcane and not easily calculated at the bedside. An electronic "app" is in the pipeline, but a nomogram should also be developed. Because about a third of patients were in the best prognostic group and a quarter of them were still alive at six months, a broader range of specific temporal and probabilistic predictions should be provided.

Because the predictions are easily affected by confounders, palliative care clinicians will need to avoid applying the tool arbitrarily. For example, a prediction of "days" that would be accurate for a natural death at home would probably be inaccurate in an acutely ill patient who is admitted to hospital with a life threatening complication and opts for aggressive life sustaining treatment in the intensive care unit.

Ultimately, however, even a state of the art prognostic tool like the Prognosis in Palliative care Study (PiPS) predictor model will often be inaccurate. This is not surprising because previous work indicated that the kind of variables evaluated in this model fail to explain a large proportion of the variance seen in actual survival.[7] New prognostic factors need to be identified and evaluated. A starting point would be to look at cases where expert clinicians formulated different prognoses from the tool. Outlier cases that fall at the extremes of the survival curves may also provide insights that minimise the amount of unexplained error in future prognostic models.

Until this inherent inaccuracy is mitigated, doctors will continue to resist prognosticating; those who do will be scorned by their colleagues and accused of "playing God." Patients' preferences for prognostic information vary during the course of the illness, so communicating the prediction to the patient is as important as forecasting it.[12]

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Speech and language delays in preschool children

Parents need readily available information so they can spot early problems

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RESEARCH, p 460

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Speech and language delays affect 6-7% of children at school entry and can result in problems in one or more areas, such as understanding vocabulary and grammar, inferring meaning, expressive language, sound production, voice, fluency and articulation, and the use of language in social contexts.[1] For some children, language problems are markers for—and secondary to—conditions such as autism, sensory impairment, or more general developmental disabilities. For others, they are the result of primary delay that cannot be accounted for by low non-verbal ability, hearing impairment, behaviour problems, emotional problems, or neurological impairments. Environmental factors such as limited opportunities for learning language or learning English as an additional language may also overlap with primary and secondary delay. In the linked cluster randomised trial, Wake and colleagues assess the effects of a low intensity parent-toddler language promotion programme delivered to toddlers identified as slow to talk on screening in universal services.[2]

Language delay that persists until school entry can have adverse effects on literacy, behaviour, social development, and mental health into adulthood, with receptive language and secondary delay particular risk factors.[3-6] But the case for secondary prevention—the early identification of language delay and early intervention before specialist investigation—is not clear cut. Firstly, variability in language development makes it difficult to identify delay early. For example, 50-60% of untreated 2 year old children who present with primary expressive language delay may be expected to "catch up" with their typically developing peers over the ensuing 12 months.[7] Secondly, although systematic reviews show that interventions can have a short term positive effect on language delay in young preschool children relative to untreated controls—particularly for difficulties in phonology, expressive vocabulary, and auditory comprehension—only a few large scale studies have been reported.[8 9]

Wake and colleagues' study conducted in Australia is thus of particular interest.[2] The study was a cluster randomised controlled trial of a community based programme to promote the language skills of young children who are slow to talk. Children who scored below the 20th centile at 18 months on a standardised parent reported checklist of expressive language were randomised to an intervention group (n=158) or to a usual care control group (n=143). The intervention comprised six two hour group based training sessions for parents, which included coaching using videotapes of the parent and child to encourage effective child centred interaction over a six week period. The study found no significant differences between groups in parent reported measures of expressive language and behaviour or blinded assessment of expressive and receptive language by professionals using standardised tests at 2 years and 3 years of age.

Despite these results, the study provides insight into the feasibility of a secondary prevention programme for language disorders. This large scale population based study cost $A895 (£568; €645; $917) per family, targeted parents who were worried about their children's language development, and included children who were learning English as an additional language.

Although parents randomised to the intervention reported that they found the programme both "acceptable" and "feasible" in terms of its implementation, 43% attended fewer than half of the available sessions and only 57% attended four or more sessions. Furthermore, it was evident from the mean standard scores for expressive and receptive language at 3 years that many of the participants randomised to the control group who presented with expressive vocabulary delay at 18 months had caught up with their typically developing peers at 3 years.

The authors identify the limitations of the study. The children may have been too young to identify language delay accurately, given the wide developmental trajectories at 18 months and the sensitivity and specificity of the language measures available. The low intensity and duration of the six week intervention as well as variable levels of parental engagement might also have contributed to the lack of effect.

In terms of the implications for practice, the study highlights the importance of well designed clinical trials to inform the best use of resources. It is also clear that the early and reliable identification of language delay under 2 years of age is problematic in all but the most severe cases. A population based approach may therefore not be the most effective way to proceed. General practitioners, health visitors, and professionals involved in the

early years should ensure that information about typical child development and milestones is readily available to parents. This can provide a basis for eliciting parents' concerns about their children's speech and language and for providing advice and support. In the United Kingdom, websites of charities such as Afasic (www.afasic.org.uk), I CAN (www.ican.org.uk), and the National Literacy Trust (www.literacytrust.org.uk) provide helpful guidance for parents about language development and how to encourage it. Referral by the general practitioner for specialist speech and language advice or triage assessment would be warranted if the problems are severe, perhaps involving not only sound production or expressive language but also marked difficulties in comprehension, social communication, and social interaction. Developmental checklists and other diagnostic tests could be used by general practitioners and health visitors to clarify the nature and severity of problems to inform decisions about whether to refer on or monitor the child's progress.[10 11]

Future research should include well designed controlled studies with economic evaluation to assess the most effective intensity and duration of intervention programmes for speech and language delay in the early years, particularly those involving parental engagement. In parallel, observational studies could further assess the effects of risk factors including receptive delay and learning English as an additional language.

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Health inequalities and cystic fibrosis

Even for genetic diseases, social conditions are still key determinants of outcome

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RESEARCH, p 461

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Domhnall MacAuley: The silence next door

Cystic fibrosis is the most common serious inherited disease in white populations. Intensive support from family and healthcare services is needed from the time of diagnosis onwards, and most patients die prematurely from respiratory failure. Survival has dramatically improved over successive birth cohorts, such that British children born in the 21st century will have a median survival of over 50 years.[1] However, disease progression and survival still vary greatly, mostly as a result of social and environmental, rather than genetic, determinants.[2] It has been known for more than 20 years that people with cystic fibrosis from socioeconomically disadvantaged backgrounds die younger than those in more advantaged positions.[3]

In a linked observational study, Barr and colleagues used death registration data in England and Wales to show that this socioeconomic divide in premature mortality in cystic fibrosis has persisted with no substantial narrowing for over four decades.[4] They also show that female patients continue to die at a younger age than male patients. What can we learn from this, and what are the implications for policy and for clinicians?

Cystic fibrosis offers a valuable case for understanding how health inequalities develop. It is an autosomal recessive disease with an asymptomatic (and, until recently, undetectable) carrier state, so unlike many other diseases, socioeconomic status does not influence who gets the disease. Inequalities related to socioeconomic status result from the different patterns of exposure to harmful and protective or therapeutic influences that occur over the course of people's lives. Studies from the United States and United Kingdom show that significant inequalities in key intermediate outcomes in cystic fibrosis, such as growth and lung function, begin early in childhood and persist over time.[5 6] The early appearance and persistence of inequalities support the need for interventions that are targeted at the early (and perhaps prenatal) years and reinforce the importance of screening for cystic fibrosis in newborns. This, incidentally, is also true for sex related inequalities, which are probably caused as much by socially determined gender roles as by biologically determined sex characteristics.[7]

A key question for practising clinicians is what role healthcare delivery plays in mitigating or potentiating health inequalities in cystic fibrosis. In the US, studies have failed to identify important socioeconomic status related differences in the use of chronic treatment for cystic fibrosis, treatment of pulmonary exacerbations, or hospital admissions,[2 5 8] although there is some evidence that affluent groups may be earlier recipients of newly developed cystic fibrosis drugs.[8] The adoption of system based methods to optimise consistency in the use of best care practices might help to minimise variations in prescribed care.[9] Other than tackling any residual socioeconomic status related differences in access and provision of healthcare to patients with cystic fibrosis, how else can inequalities be reduced?

Some underused tools are available to cystic fibrosis clinicians. One obvious target for action is to protect newly diagnosed children from environmental tobacco smoke. There are striking and persistent differences in the prevalence of

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smoking according to socioeconomic status.[10] Exposure to environmental tobacco smoke is associated with poorer growth and lung function in cystic fibrosis,[2] and it may be the most important explanatory factor for inequalities related to socioeconomic status in this disease.[11] Early identification of family members who smoke, and appropriate counselling and referral to smoking cessation services, would be an effective intervention for all patients, regardless of social position. This should be coupled with support to develop disease self management skills in the patient and the family,[12] in addition to targeted input from social workers who work with the multidisciplinary cystic fibrosis team.

Ultimately, however, although individually focused interventions may have some limited success, the more effective long term solution to health inequalities in people with cystic fibrosis and in the general population is likely to be one that takes broader action to tackle the social determinants of health. These are the "conditions in which we are born, grow up, work, and live," and they include income and income distribution, education, employment and working conditions, housing, food insecurity, race and ethnicity, and sex and gender roles. These factors provide a particularly important context for a family dealing with the stresses of caring for a child with a complex chronic illness like cystic fibrosis over a lifetime.

The evidence is clear, unfortunately, that we have made little progress over the past few decades in reducing health inequalities generated by social gradients,[11] and this evidence is strengthened by Barr and colleagues' study. Future research should assess the mechanisms that generate socioeconomic status related inequalities and the interventions that are most likely to reduce them, bearing in mind that investigating interventions at the population level is likely to have greater impact. The current political discourse in the US suggests that any insight into effective social interventions is unlikely to come from that side of the Atlantic; the discussion on the UK side, inspired by documents such as the Marmot report,[11] will hopefully provide a first step towards investigating and putting into practice the most effective ways to reduce the socioeconomic gradient in health.

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Maternal mortality and the need for obstetric physicians

Most UK deaths are now caused by preventable or treatable medical conditions

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Since the first report of the Confidential Enquiry into Maternal Deaths in 1952, the maternal death rate in the United Kingdom has decreased dramatically.[1] This has been due to an impressive fall in deaths with direct obstetric causes, including obstetric haemorrhage, ectopic pregnancy, and venous thromboembolism. This has partly been achieved through better understanding of obstetric complications, advances in medical treatments, and the use of evidence based guidelines that implement recommendations made in previous reports.[2] However, almost 60 years since the first Confidential Enquiry into Maternal Deaths report, the most recent report, published in March 2011, highlights a worrying trend in the causes of maternal mortality in the UK.[1]

The report states that most maternal deaths in the UK now occur in women with pre-existing or new onset medical and psychiatric conditions ("indirect causes"). The leading cause of maternal death remains cardiac disease; the second is neurological disease. Most worryingly, the number of maternal deaths from indirect causes has significantly increased over the past 20 years (table). Furthermore, most of these deaths are associated with substandard care, and in one third of cases this is classified as major substandard care, where different care might have prevented death of the mother. These failings require urgent attention.

Much has been written about the failure to achieve the United Nations' fifth millennium development goal to reduce the maternal mortality ratio by three quarters by 2015.[3] But it is under-appreciated that even in the UK women die in pregnancy or shortly after delivery from preventable and treatable medical causes such as epilepsy, diabetes, heart failure, and asthma.

Past and present Confidential Enquiry into Maternal Deaths reports have repeatedly shown that factors contributing to substandard care include failure to appropriately diagnose, investigate, and treat women with new onset chest pain, headache, or other medical symptoms.[1] This often arises when well meaning clinicians prioritise the health of the fetus over that of the mother, but it can result in the death of both mother and fetus.

Changes in maternal direct and indirect death rates in the UK*

	Years	
	1985-7	2006-8
Direct death rate (per 100 000 maternities)	6.13; 5.19 to 7.23	4.67; 3.86 to 5.64
Indirect death rate (per 100 000 maternities)	3.7; 2.99 to 4.58	6.72; 5.74 to 7.87

Figures are mean; 95% confidence interval.

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Obstetricians and midwives alone cannot reduce indirect maternal deaths—they need support from physicians and general practitioners. But many doctors are unfamiliar with the interaction between pregnancy and medical disease, the safety of radiological investigations in pregnancy, and the risk-benefit ratio for the use of different drugs in pregnancy. During the three years that the current report is based on (2006-8), one woman died from asthma after her general practitioner advised her to stop taking oral prednisolone.[1] In many cases pre-pregnancy counselling was not given to women with pre-existing medical conditions, so that they entered pregnancy not understanding their risks or how their management could be optimised.

Specific recommendations from the latest report include:

- All women planning pregnancies that are likely to be complicated by potentially serious medical conditions should have pre-pregnancy counselling
- Women whose pregnancies are complicated by potentially serious medical conditions should be referred to appropriate specialist centres of expertise, where both care for their medical condition and their obstetric care can be optimised
- Doctors who do not work directly with pregnant women need to know more about the interaction between the conditions that they are treating and pregnancy.[1]

Doctors and general practitioners looking after pregnant women in clinics or in acute settings need to have the skills to assess the common symptoms of pregnancy including breathlessness, headache, and epigastric pain. These are mostly benign, but they can herald or represent fatal disease. A "back to basics" section of the latest report highlights the "red flags" for these symptoms.[4] It is not clear who is going to provide the pre-pregnancy counselling recommended in the report—the general practitioner, the woman's own doctor, or an obstetrician?

Increasing numbers of women with often complex medical conditions are now becoming pregnant or seeking fertility treatment. Women are delaying childbearing until later in life, and the menopause is no longer a barrier to pregnancy. Older women are more likely to be obese, have hypertension, or be predisposed to gestational diabetes and thromboembolism. The success of modern medicine, surgery, and transplantation in treating conditions that previously would have precluded pregnancy has led to increasing numbers of "high risk" pregnancies in women with chronic medical disorders. Furthermore, migrant women present with disorders such as rheumatic heart disease or tuberculosis that can cause complications in pregnancy. These women require expert and informed pre-pregnancy counselling and expert multidisciplinary care during and after pregnancy to optimise both maternal and fetal outcomes.

The data and recommendations from the confidential inquiries report suggest that the training of obstetric physicians and their numbers should be expanded and that the subspecialty should be formally recognised. Obstetric physicians specialise in the care of women with pre-existing and new onset medical problems in pregnancy, and much of their work involves specialised pre-pregnancy counselling. Most surgical specialties have medical counterparts (neurosurgery, urology, cardiac surgery), but not obstetrics. Moreover, many other countries, including Canada, the United States, Australia, and New Zealand, recognise the importance of obstetric medicine and have well developed training programmes.[5]

The expansion of obstetric anaesthesia was associated with an impressive fall in anaesthesia related deaths in pregnancy. The current maternal death figures show a need to involve medical skills. An expansion in the number of obstetric physicians would be a positive step towards reducing deaths from medical disorders in pregnancy. Not every obstetric unit needs an obstetric physician, but they all need access to one, perhaps within maternity networks. Such a specialist in each region would ensure that when obstetricians, physicians, or general practitioners confront difficult or complex medical problems in pregnancy they will have easy access to an expert opinion. In addition, obstetric medicine should form part of the postgraduate training curriculum of general practitioners and physicians, as already happens in the US, Canada, Australia, and New Zealand.

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Androgen deprivation therapy for prostate cancer

Cardiovascular risk should be monitored, and primary and secondary prevention optimised

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Accumulating evidence suggests that androgen deprivation therapy for prostate cancer is associated with adverse effects on cardiovascular risk factors such as diabetes, the incidence of cardiovascular events, and, in some studies, death from cardiovascular disease.[1-6] Although not all studies concur, a science advisory statement from the American Heart Association, American Cancer Society, and the American Urological Association has recommended that all patients receiving such treatment should have periodic follow-ups for assessment of cardiovascular risk factors and those with coexisting cardiovascular disease should have their treatment for secondary prevention optimised.[1]

A large follow-up study of 73 196 men (>65 years) with locoregional prostate cancer in which about a third were

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given androgen deprivation therapy reported a higher incidence of cardiovascular disease, diabetes, myocardial infarction, and sudden death from cardiac disease or life threatening ventricular arrhythmia.[2] Observational studies of men over 65 given androgen deprivation therapy have found a greater risk of fatal myocardial infarction in the first six months and death from cardiovascular disease during a mean follow-up of 3.8 years.[3 4] A study (n=22 816) reported a 20% higher risk of morbidity from cardiovascular disease within the first year of treatment.[5] Another study (n=30 642) also found that the treatment increased the relative risk of non-fatal and fatal cardiovascular disease—risk was greater in men without cardiovascular disease than in those with known disease, presumably because these men were already receiving secondary prevention measures.[6] However, not all studies—including the recently reported EORTC 22863 trial—have found an increased risk of morbidity and mortality from cardiovascular disease.[1 7] Because of the confounding evidence from studies with different designs and subject selection, and especially because the data are mainly retrospective, the findings are not conclusive.

Testosterone deficiency is associated with adverse cardiovascular risk parameters including central obesity, insulin resistance, hyperglycaemia, dyslipidaemia, hypertension, and a prothrombotic and proinflammatory milieu (all components of the metabolic syndrome).[8] Most longitudinal epidemiological community based studies show that low testosterone is associated with increased all cause mortality and death from cardiovascular disease.[8] Low testosterone was also a predictor of increased all cause and cardiovascular mortality in men with confirmed coronary heart disease over a seven year follow-up period.[9]

Androgen deprivation therapy for prostate cancer produces a severe state of hypogonadism, which results in increased central adiposity, increased proportion of body fat, and a decrease in lean body mass.[10 11] These changes mainly affect subcutaneous not visceral fat, which is atypical for the metabolic syndrome.[11] One study recorded a rise in total and low density lipoprotein-cholesterol, triglycerides, and high density lipoprotein-cholesterol after androgen deprivation therapy, but others have not.[10] Fasting insulin values rise and insulin sensitivity falls, with an increase in glycated haemoglobin (HbA_{1c}).[11 12] Importantly, a retrospective analysis of men with type 2 diabetes who were taking insulin found that androgen deprivation therapy resulted in a marked deterioration in their diabetic control, with insulin dosages needing to be increased.[12] Extra vigilance is therefore needed, especially in men with diabetes, in the early phase of treatment.

The science advisory board recommends that because of the metabolic effects of androgen deprivation therapy, patients should be referred to their primary care doctor for periodic follow-up including, when appropriate, review of lipid lowering treatment, antihypertensives, glucose lowering treatment, and antiplatelet drugs.[1] It suggests that the primary care doctor should review cardiovascular risk factors at three to six months and at least yearly thereafter. Currently, there is no indication for specific cardiological investigations or interventions. Men with pre-existing cardiovascular disease should have their secondary prevention treatment optimised. The urologist must inform the primary care doctor when androgen deprivation therapy is started and of the potential adverse effects on cardiovascular risk factors.[1] The science advisory board recommends that the doctor treating the prostate cancer should make the decision about treatment after weighing up the benefits and harms, especially in a man with known cardiovascular disease.[1]

Androgen deprivation therapy combined with radiotherapy is a widely established and effective treatment that improves outcome and survival in men with intermediate risk or high risk localised prostate cancer. The science advisory writing group believes that the risk of androgen deprivation therapy to cardiovascular health may become more apparent with the increasing length of survival of patients with prostate cancer. These findings have already led to the US Food and Drug Administration making a change to the label for gonadotrophin releasing hormone agonists in the treatment of prostate cancer (www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm230359.htm). On the basis of the current evidence, the identification and assessment of cardiovascular risk in men taking androgen deprivation therapy is an extrapolation of good clinical practice in the general population. The clinical awareness of this association could potentially improve overall survival.

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