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A differentiated approach to referrals from general practice to support early cancer diagnosis – the Danish three-legged strategy

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Abstract: When aiming to provide more expedited cancer diagnosis and treatment of cancer at an earlier stage, it is important to take into account the symptom epidemiology throughout the pathway, from first bodily sensation until the start of cancer treatment. This has implications for how primary-care providers interpret the presentation and decisions around patient management and investigation. Symptom epidemiology has consequences for how the health-care system might best be organised. This paper argues for and describes the organisation of the Danish three-legged strategy in diagnosing cancer, which includes urgent referral pathways for symptoms suspicious of a specific cancer, urgent referral to diagnostic centres when we need quick and profound evaluation of patients with nonspecific, serious symptoms and finally easy and fast access to 'No-Yes-Clinics' for cancer investigations for those patients with common symptoms in whom the diagnosis of cancer should not be missed. The organisation of the health-care system must reflect the reality of symptoms presented in primary care. The organisational change is evaluated and monitored with a comprehensive research agenda, data infrastructure and education.

In recent years, many health-care systems have implemented specific strategies to ensure timely cancer diagnosis (Department of Health, 2000; Prades *et al*, 2011). This has been motivated by poor cancer control, public discontent with long waiting times and an organisational and economic attempt for efficiency in standardised diagnostic pathways (Richards, 2009). Reports have shown that cancer survival in the United Kingdom and Denmark is lower than that in other countries (Storm *et al*, 2010; Coleman *et al*, 2011). Danish cancer patients are treated at later stages (Maringe *et al*, 2012; Walters *et al*, 2013a,b), suggesting delays in presentation, diagnosis and treatment. This is supported by the evidence that waiting times can be long in the Danish cancer care system, which may lead to higher mortality (Tørring *et al*, 2011, 2012, 2013; Elit *et al*, 2014; Redaniel *et al*, 2014; Neal *et al*, 2015) and stage progression (Jensen *et al*, 2007; Wang *et al*, 2012).

In 2008, after several years of investment in cancer treatment and two cancer plans, Denmark introduced urgent referral for suspected cancer (Olesen *et al*, 2009). Politically, cancer was proclaimed an acute disease for which diagnosis and treatment should be without waiting time (Probst *et al*, 2012). Such urgent referral pathways are in place in a number of health-care systems and are being developed in others. Based on the defined alarm

symptoms, the GP can suspect cancer and refer urgently to a specific pathway, and the speed and logistics of the diagnostic pathway and the standardisation of treatment within the hospital setting can be improved (Toustrup *et al*, 2011; Vallverdú-Cartié *et al*, 2011; Valentín-López *et al*, 2012; Dyrop *et al*, 2013; Larsen *et al*, 2013).

In the process that followed the introduction of the urgent referral pathway in Denmark, it became obvious that this pathway was inadequate to ensure timely diagnosis of all cancer patients, and a strategy based on three cornerstones was developed.

This paper argues for and describes the three-legged strategy for cancer diagnosis in Denmark, where the purpose is to accommodate the fact that patients with an early-stage cancer present very differently in general practice and that a single focus on alarm symptoms or red flags might not be sufficient.

REASONS FOR LONGER DIAGNOSTIC PATHWAYS

If cancer patients are asked, after treatment completion, what they consider the most important part of the pathway, they report aspects of expedited referral, diagnosis and treatment and short

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waiting time for all investigations, including the very first ones often prescribed by the GP (Booji *et al*, 2013). This is also indicated by the finding that Danish cancer patients' confidence in their GPs decreases with increasing time to diagnosis (Larsen *et al*, 2011).

A study among Danish GPs in 2010, after the introduction of urgent referral for suspected cancer, asked about their cancer patients, diagnostic pathways, and showed that in about one-third of cases, the GPs reported a quality deviation which was strongly associated with longer diagnostic intervals (Jensen *et al*, 2014).

There is also evidence that the organisation of the health-care system may have adverse effects. In an ecological study in which we compared a number of European countries' primary care and their 1-year cancer survival rates, we saw that countries with a strong gatekeeper role also had the lowest cancer survival rates (Vedsted and Olesen, 2011). This could suggest that in some countries where GPs were good gatekeepers, the GPs had become too reluctant to refer early to diagnostic investigations. Further, that access to diagnostic services in the initial phase was slow or rationed, resulting in patients not obtaining timely cancer investigations.

SYMPTOM EPIDEMIOLOGY AND THE 'DIAGNOSTIC FUNNEL'

Another aspect is that health-care systems should be organised to support the diagnostic needs. In cancer diagnosis, the processes related to symptom epidemiology must be recalled (Figure 1; Elliott *et al*, 2011). In line with this, studies have demonstrated the 'symptom iceberg', showing that >15% of adults will have experienced at least one cancer alarm symptom during the last year (Svendsen *et al*, 2010). Only a small proportion of these will seek help, for example 10% of those with rectal bleeding consult their GP (McAvoy, 2007).

Despite relevant screening activities, ~85–90% of all cancers are diagnosed on the basis of symptomatic presentation (Hansen *et al*, 2011; Vedsted and Olesen, 2009; Emery *et al*, 2014). In health-care systems in which GPs form a specialised first line, data show that 75–85% of all cancer patients start in general practice by presenting signs or symptoms (Allgar and Neal, 2005).

It has been shown that the GP indicates potential alarm symptoms in up to 12% (Ingebrigsten *et al*, 2013) of all consultations and suspect a serious disease in need of further elucidation in 6% of consultations (Hjertholm *et al*, 2014) (Figure 1). A study showed that 10% of these patients had a new serious diagnosis within 2 months. This means that when the GP

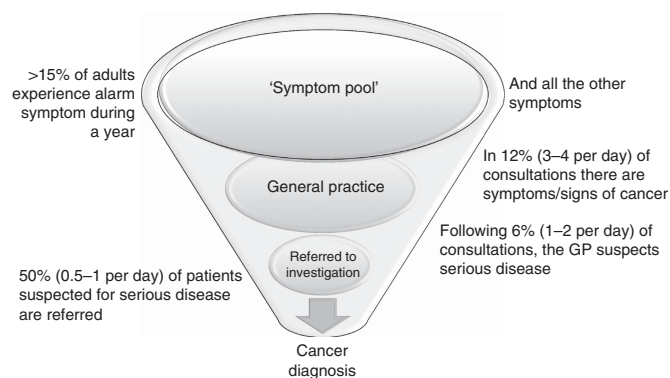


Figure 1. The diagnostic funnel showing the symptom epidemiology from public to cancer diagnosis. General practice is placed between the public 'symptom pool' and the decision to investigate for cancer.

suspects serious illness there are reasons to support the GP in having access to relevant investigations (Nylenna, 1986).

THE SYMPTOM CONTINUUM

Another important aspect is that, once a symptom is presented in general practice, the severity of a symptom could be thought of as forming a continuum. An example of this continuum could be abdominal pain. In the clinical context, abdominal pain should be understood in terms of the continuum with increasing clinical significance, thus becoming more and more indicative of a serious disease (cancer). In the clinical cancer diagnosis, a symptom does not present as 'there' or 'not there'. Symptoms appear from 'certainly not serious' to 'definitely serious' (Figure 2).

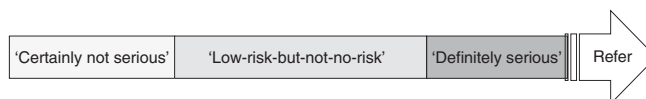


Figure 2. The symptom continuum in general practice. A symptom can present clinically in many ways.

The first section (left) of the symptom continuum is that in which the symptom presents as harmless. The second section is where the symptom is most probably not a sign of cancer, although cancer cannot be excluded. This is the so-called 'low-risk-but-not-no-risk' symptom (Hamilton, 2010). The third section is where the symptom definitely indicates risk of a serious disease and an urgent referral is relevant. Fortunately, in general practice it is rarely cancer, even if it is an alarm symptom (Hamilton, 2009a). However, it is still the GP's duty to identify the cancer over the whole symptom continuum. Progression along the symptom continuum might, for example, be the reason that we can observe that patients who are later diagnosed with cancer tend to see their GP several months before diagnosis (Christensen *et al*, 2012; Ahrensberg *et al*, 2013). Here the GPs may have used time as a diagnostic test (Almond and Summerton, 2009). However, waiting until the symptom becomes definitely serious might also imply a stage progression in some cancers.

THE 'OBVIOUS', 'DIFFICULT' AND 'COMMON' CANCER PRESENTATIONS

A study in Danish general practice has revealed that, if GPs are allowed simply to categorise the first presentation of cancer, 50% are categorised as alarm symptoms, 20% are serious, but cancer nonspecific symptoms and 30% are categorised as normal vague symptoms (Jensen *et al*, 2014). This has also been supported by the finding that 50% of cancer patients in United Kingdom general practice did not have a National Institute for Health and Care Excellence guideline symptom suspicious for cancer registered in the patient record (Neal *et al*, 2014). Thus, some cancer patients do present in general practice, but not with symptoms indicative of cancer.

THE THREE-LEGGED DIAGNOSTIC STRATEGY

A wish for expedited cancer diagnosis and cancer diagnosis at an earlier stage necessitates that we broaden the focus on alarm symptoms to include the full symptom continuum. A system that focusses on cancer diagnosis based on alarm symptoms alone might also be a health-care system that favours 'the sick-quick' and lets down the majority with vague symptoms (Hamilton, 2009a).

A Danish study illustrated this by showing that, if the GP regards the symptom as vague, 50% of cancer patients will wait at least one month more and 25% at least 2.5 months longer until diagnosis, compared with those with alarm symptoms (Jensen *et al*, 2014). Thus, urgent referral for the obvious alarm symptoms must be accompanied by two more referral routes; the urgent referral for nonspecific, serious symptoms and the no-yes-clinics (NYC).

This led to the development of the three-legged cancer diagnosis strategy in Denmark (Figure 3). It acknowledges that we need diagnostic routes for what the GPs recognise as alarm symptoms (the obvious cancer suspicion), the nonspecific symptoms (the difficult diagnosis) and the vague symptoms (the common symptom).

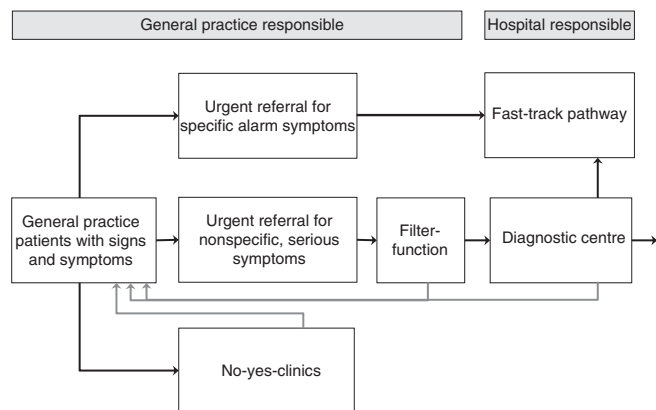


Figure 3. The structure of the Danish three-legged diagnostic strategy.

THE URGENT REFERRAL PATHWAY

From UK-based practice research, it is known that the risk of having cancer given a single alarm symptom is often in the range of 3–8% (Jones *et al*, 2007; Hamilton, 2009b; Shapley *et al*, 2010). Meechan and colleagues (2012) showed that, among those referred to the urgent referral pathway, the risk of cancer was 11%. Thus, the urgent referral strategy seems to be effective. However, what is also shown – and forms the platform for introducing further diagnostic possibilities – is that on average only 40–45% (with differences between cancer types) of all cancer patients are primarily referred to specific pathways (Meechan *et al*, 2012; Jensen *et al*, 2014). This means that the largest group of cancer patients is not offered this faster and perhaps most appropriate route to diagnosis (Elliss-Brookes *et al*, 2012; GuldbRANDT *et al*, 2015).

URGENT REFERRAL FOR UNSPECIFIC, SERIOUS SYMPTOMS AND THE DIAGNOSTIC CENTRES

The urgent referral for unspecific, serious symptoms was implemented nationally by the National Board of Health and Danish Regions in 2012. When a GP has a patient that is clearly sick, and where cancer is one of several diagnostic possibilities, they can be referred. The pathway consists of a two-step approach with a filter function performed by the GP and, if still relevant, a referral to a diagnostic centre. The filter function is a standard battery of diagnostic investigations consisting of blood and urine tests and diagnostic imaging. The results of the investigations are sent electronically to the GP within four working days. The GP subsequently decides further diagnostic steps within eight working

days. If there is no explanation for the symptoms the GP can refer to the diagnostic centre and no longer has the diagnostic responsibility for the patient.

A diagnostic centre is a medical unit with comprehensive facilities for medical investigation, including easy access to expertise in a wide range of relevant specialities. Patients are appointed a responsible doctor for the outpatient trajectory.

Each of the five Danish regions must have at least one diagnostic centre, and ~15 centres have now been established. The symptoms most often seen at referral are weight loss, fatigue, unspecific pain and nausea. ‘Problems with general health’ and ‘GP’s gut feeling’ are among the most likely clinical signs for referral to a diagnostic centre. The proportion with cancer among those referred is ~15–20%. The cancers most often seen are lung, colorectal and haematological cancers. There are ongoing publications of these specific results.

THE NYC

For the 30–40% of cancer patients with vague, ‘low-risk-but-not-no-risk’, symptoms, Denmark now, by a governmental regulation, implements the ‘NYC’. These are services conducted in hospitals or specialist clinics. The GP has direct access to fast investigations as part of the classical iterative diagnostic process (Norman *et al*, 2009) where the GP can raise a possibility of cancer – the serious diagnosis that the GP does not want to fail to spot.

The principle is to keep it simple; the GP is responsible for the diagnostic actions and the patient is not admitted to the hospital, thus avoiding use of resources, for example, history taking, blood tests, patient records and other administrative or clinical resources demanding activity. Studies indicate that the strategy can be both effective and efficient. A Dutch study of direct access to colonoscopy for abdominal symptoms showed reduced time to diagnosis and more efficient use of tests (Klemann *et al*, 2011). This is supported by studies from the United Kingdom (Maruthachalam *et al*, 2005; Ahmed *et al*, 2013). A randomised Danish study giving GPs direct access to a low-dose CT scan for suspected lung cancer showed that the use of CT scans did not increase, compared with the usual ‘double gatekeeping’ by the lung specialist (GuldbRANDT *et al*, 2013).

There are ongoing studies on the specific ways of organising this, which patients to refer and what investigations should be provided.

CONCLUSION AND PERSPECTIVES

When aiming to provide more expedited cancer diagnosis and treatment of cancer at an earlier stage, it is important to take into account the symptom epidemiology throughout the pathway, from the first bodily sensation until the start of cancer treatment. This has implications for how primary care providers interpret the presentation and decisions around patient management and investigation. Symptom epidemiology has consequences for how the health-care system might best be organised.

This paper provides several reasons to support and test a three-legged strategy, in particular for diagnosing cancer in earlier stages. The GPs need diagnostic routes that, first, take into account the fact that symptoms present on a continuum from ‘certainly not serious’ to ‘definitely serious’ and, second, that cancers present with symptoms that sometimes obviously indicate cancer but for the majority are nonspecific and serious or vague and common. Since our previous paper in 2009 about the Danish example (Olesen *et al*, 2009), the focus in Denmark has been to develop broad support for the GPs’ different tasks in diagnosing cancer.

The continuous growing evidence on cancer diagnosis is implemented into daily clinical practice and health policy to ensure structural support. Thus, it should be remembered that in a modern health-care system the best pathways from symptom to cancer treatment are established only if there is a culture of responsibility – making these changes requires political, administrative and clinical leadership.

To improve and optimise this differentiated approach we call for a large research agenda and precise evidence-based implementation strategies. The effectiveness and efficiency of the diagnostic centres and the NYC need further research and monitoring, and the Danish government and regions are engaged in this work. Intervention studies are needed to test whether there is an effect on stage distribution and survival, quality of life, health economics and patient evaluation. There is a need for more clinical research, including research into primary care and specialised diagnostic investigations. Finally, we must also ensure practical implementation by education (Guldbrandt *et al*, 2014) and facilities for primary diagnosis (Toftegaard *et al*, 2014).

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CONFLICT OF INTEREST

FO is the chairman of the Danish Cancer Society (2015). PV declares no conflict of interest.

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