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Health Enterprise East

EARLY DIAGNOSIS & DETECTION OF CANCER

A HEALTH ECONOMIST'S PERSPECTIVE

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About the Medtech Navigator

The Medtech Navigator, part-funded by the European Regional Development Fund (ERDF), is a three-year programme, delivered by Health Enterprise East Ltd., to facilitate knowledge exchange between the medtech industry, many of whom are small and medium sized enterprises (SMEs), the NHS, and academia. The programme seeks to enable companies to identify potential market opportunities in a variety of specific disease areas and apply for Innovation Grant funding through the programme, thereby engaging SMEs in new R&D projects that are both customer-focussed and collaborative in nature. This will allow the creation of partnerships between clinicians, academics and industry to develop novel medical technologies which will improve healthcare and quality of life for patients and the healthcare market of the future.

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At Health Enterprise East believe in improving healthcare through technology and innovation.

We work with the NHS, medical technology industry and government organisations to help turn innovative ideas into products and services that will benefit patients.

Our experienced team offers clients a diverse range of business and innovation management services. Our strengths include IP management, technology commercialisation, health economics and strategic market access advice.

Based in Cambridge, we work with over 25 NHS organisations nationally and medtech companies globally. Our aim is to help our clients address the challenges faced along the product development pathway, connecting them with relevant healthcare experts and funding opportunities.

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Introduction & Abstract

Though cancer has been around throughout most of human recorded history, it is only recently, as the demographic composition of the human population has changed, that it emerged as a leading cause of death.

Cancer can be prevented, and its impact reduced if caught early. This is why early detection and diagnosis has been recommended as one of the key strategies in tacking the societal burden imposed by cancer. While the clinical benefits of early detection are evident, the health economic aspects are less clear-cut.

As health economists are evaluating the different diagnostic interventions employed by healthcare systems, a patchwork of different outcomes emerges, where some diagnostic interventions prove themselves to be cost-effective, while others are less so. This whitepaper discusses the advantages and disadvantages of various diagnostic strategies and makes the case for better use of data sourced from secondary care, primary care, genomic profiling as well as user-generated data from consumer devices and the Internet of Things (IoT) to identify high-risk individuals early on. The diagnostic technologies used to test at-risk patients need to strike a delicate balance between diagnostic accuracy and cost to the healthcare system. Cost-effectiveness can differ by type of cancer and the effectiveness of the treatment options available.

The challenges thrown up by the Covid-19 pandemic are expected to accelerate the expansion of diagnostic capacity in the UK as well as drive uptake of telemedicine, artificial intelligence (AI) and improvement in triaging tools. Future cancer care is forecast to be dominated by the identification of high-risk individuals and preventative interventions. For those patients diagnosed, managing the condition will become more akin to managing a chronic condition. Easy-to-use technologies for monitoring and surveillance of the progression of the disease will be important pillar stones of future cancer care with liquid biopsy testing expected to play a significant role. Ultimately the diagnostic technologies need to facilitate improved decision making by clinicians and public health officials to lessen cancer's impact on society.

Cancer and its burden on society

Cancer has been around for most of human recorded history, with some of the earliest evidence found among fossilised human bone tumours, mummies in ancient Egypt as well as ancient manuscripts[1]. However, for much of human history, cancer was not an issue as people did not live long enough for it to impact their lives in any meaningful way.

As the demographics of the world population have changed, population health changed along with it; alteration in age composition, migration, lifestyle, population density and urban-rural movement has required adaptation of healthcare delivery to address the new problems thus created. The confluence of these factors has conspired to make cancer a leading cause of death worldwide according to the World Health Organisation (WHO) and the most important challenge facing healthcare systems today with the annual number of new cancer cases projected to increase from 14.1 million in 2012 to 21.6 million by 2030[2].

From a macro-economic point of view, the economic burden it imposes on UK society in terms of lost productivity is substantial (*Figure 1*).

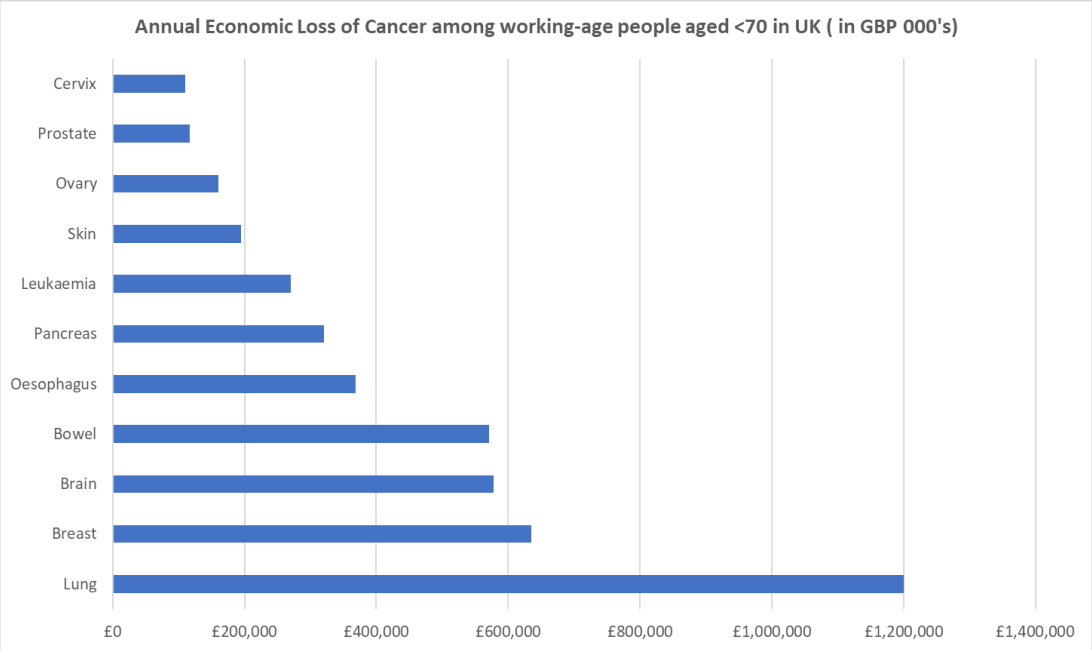

Figure 1 - Annual Economic Loss of Cancer as measured by the human capital approach in the UK[3]

Cancer can be prevented; public health interventions to reduce exposure to risk factors and incentivise changes in lifestyle combined with early detection and diagnosis can significantly reduce incidence and mortality from cancer.

Diagnostic testing and its impact on health outcomes

The World Health Organisation recommends early diagnosis and screening to detect and treat cancers earlier. NHS England's Long-Term Plan has committed to detect 75% of cancer at an early stage by 2028[4]. The new cancer diagnosis roadmap recently published by Cancer Research UK makes early detection and diagnosis the main focus for improving health outcomes and saving lives[7].

A diagnostic test itself, however, does not lead to improved health; it is the decisions taken based on the outcomes of the test and the available therapeutic treatment options which impact health outcomes (see *Figure 2*).

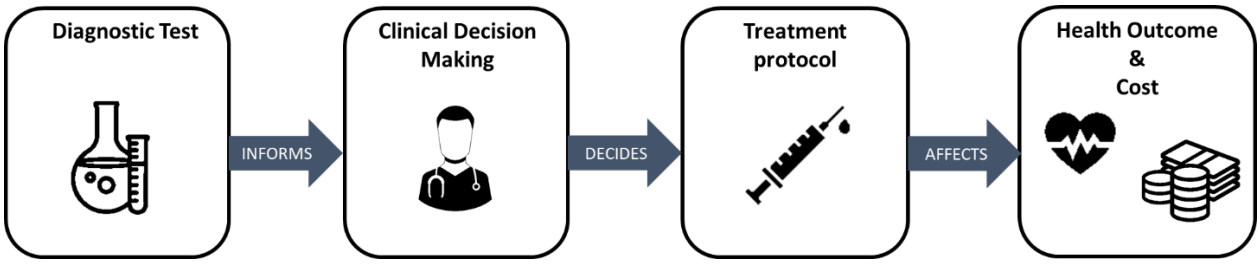

Figure 2 - Cost-effectiveness of diagnostic testing

Early detection and diagnosis of cancers will only lead to better outcomes if the treatment regimens available can lead to improved health outcomes over the lifetimes of the patients diagnosed.

The high levels of uncertainty involved in extrapolating long-term outcomes for cancer patients and the preponderance of potential confounding factors coming into play when trying to forecast a patient's health trajectory, over his or her lifetime, make establishing a causal link between early diagnosis and improved health outcomes difficult.

As health economists are evaluating the different early detection and diagnostic interventions employed by healthcare systems, a patchwork of different outcomes emerges, where some diagnostic interventions prove themselves to be cost-effective, while others are less so. The factors influencing these outcomes are the cost and accuracy of the diagnostic technology itself, the prevalence of the type of cancer, the characteristics of the susceptible patient population, as well as the cost and effectiveness of the treatment options available. As some of the pharmaceutical cancer treatments lose their patent protection and prices fall, with the entry of generics, the cost-effectiveness of the programmes may change.

Large-scale population screening programmes tend to be less cost-effective as they tend to hoover up a significant share of the healthcare budget. A national screening programme such as the bowel screening programme for bowel cancer costs GBP211 million per year[5]. This is money which is no longer available to the healthcare system to purchase other healthcare services and interventions for other patients. The question is whether the outcomes achieved by such screening programmes produce more population health as measured in life years and health-related quality of life than other interventions may have produced with the same amount of money. This "opportunity cost" needs to be assessed to ensure that public funds raised via taxes are spent in the most cost-efficient way and with maximum transparency. An evaluation of the NHS breast screening programme, for example, found it only had a 45% to 60% probability of being cost-effective at the cost-effectiveness thresholds employed by the National Institute for Clinical Excellence (NICE)[6].

Early detection & diagnosis

Early detection and diagnosis of cancer, as advocated by Cancer Research UK[7], recommends both screening and early diagnosis as important components of cancer control. However, screening and early diagnosis are two very different approaches (*Figure 3*) with different resource and infrastructure requirements, impact and cost;

- Early diagnosis is the testing of people who have symptoms and signs indicative of cancer. The objective is to identify the disease as early as possible to move quickly to treatment. When cancer is detected at a potentially curable stage, healthcare outcomes can drastically be improved
- Screening aims to identify unrecognised cancer, or its precursor lesions in an apparently healthy, asymptomatic population by means of tests, examinations, imaging, or other procedures that can be applied rapidly and accessed widely by the target population. The NHS currently screens for three types of cancer: breast, cervical and bowel.

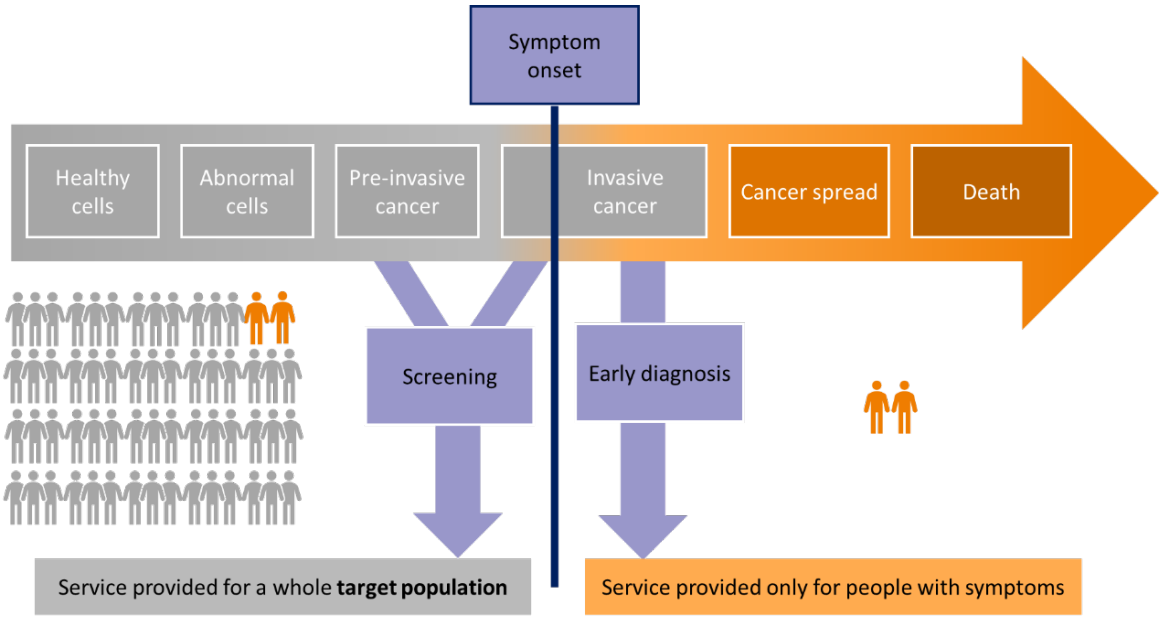

Figure 3 - Distinguishing Screening from Early Diagnosis – Diagram courtesy of WHO[8]

A screening programme tends to test an entire target population, and most individuals will not have the disease. With a few exceptions, screening programmes do not diagnose a condition; patients who test positive require further evaluation with subsequent diagnostic tests. Screening programmes are expensive to administer as they encompass the entire process from invitation through to treatment and require national planning, coordination, monitoring and evaluation. Some early cancers detected in this way may show longer survival times simply by the fact that they were detected earlier, even though there is no causality between this and longer survival times; this is known as “lead-time bias”(*Figure 4)*.

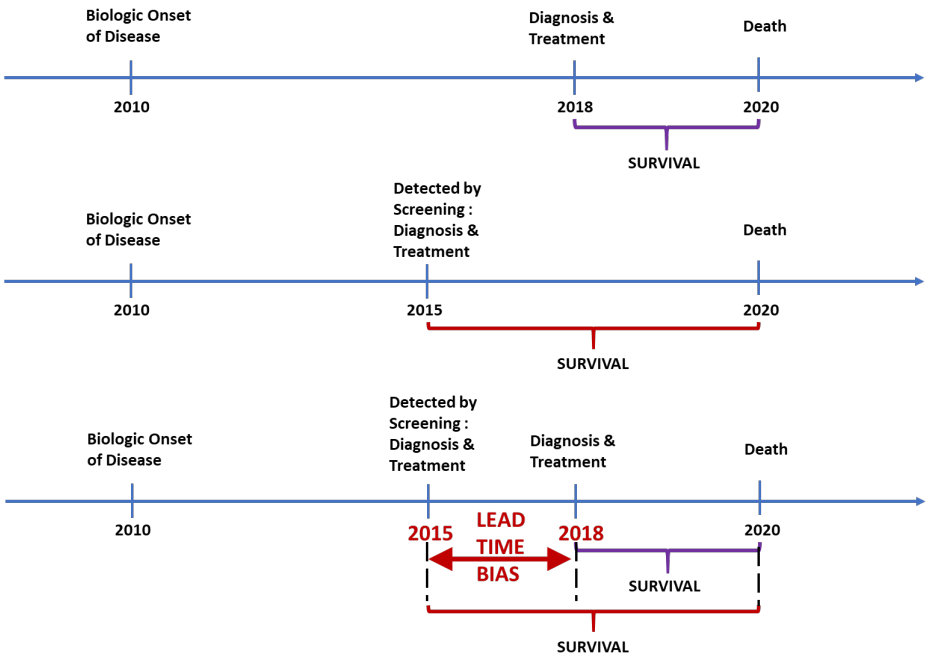

Figure 4 - Lead Time Bias as represented by L.Gordis[9]

Early diagnosis requires the patient to be aware of early symptoms and seek out a consultation with a primary care physician. After examination of the patient, testing can then either done at primary care, or by referral to secondary care. Early diagnosis is not as expensive as screening but imposes an additional burden on the primary care physician, especially in disease with low prevalence rates and could result in primary care practices being overwhelmed with extra patients who don't need to be there, reducing the quality of care for those who do. Because early diagnosis relies on the patient to seek out a physician, this strategy can often show worse health outcomes as patients with more severe symptoms and worse prognosis tend to be the most obvious cases and are therefore diagnosed sooner. In this case, there is inverse causality between disease severity and diagnostic delay.

Technology gap and opportunities for improved identification of high-risk patients

In between the strategies of screening and early diagnosis exists a notable technology gap; patients who are high-risk, but without symptoms or early symptoms and who would not seek out a healthcare professional (*Figure 5*); for example, patients with a specific family history and/or specific genotypes which increases their risk of developing cancer.

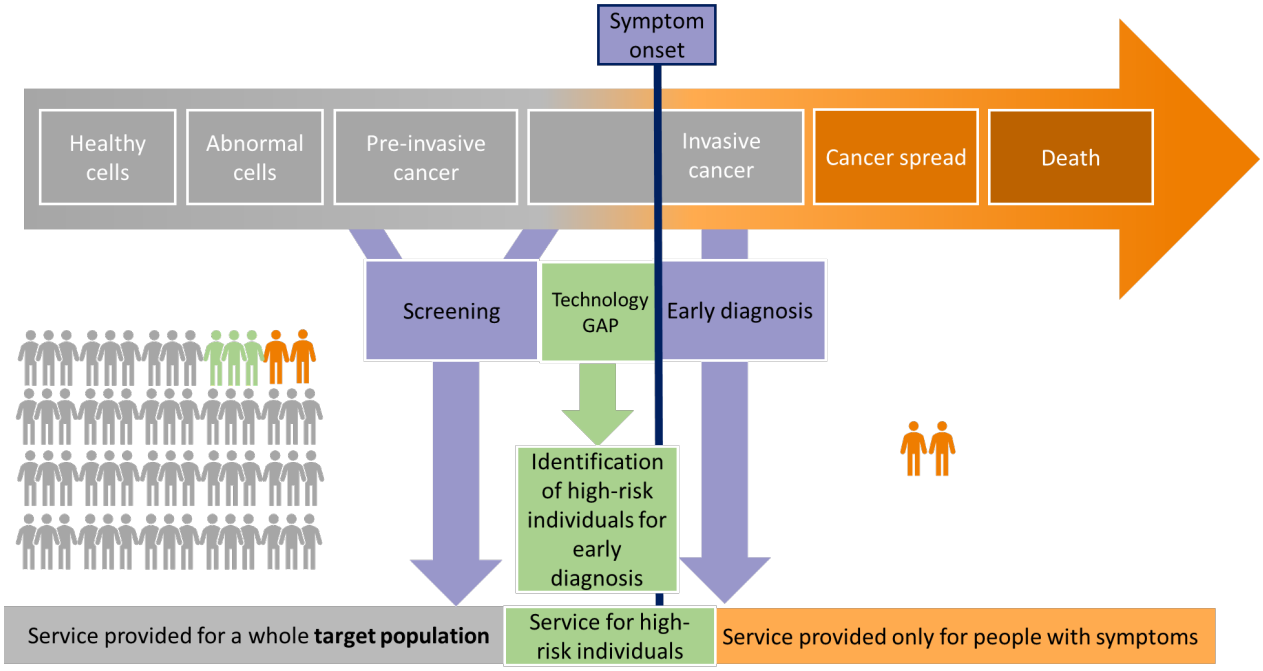

Figure 5- Technology Gap between Screening and Early Diagnosis

Though electronic health records (EHR) are already being used to flag up high-risk individuals, use of existing data to triage individuals is still in its infancy in the healthcare space.

A novel approach is needed to amalgamate data from primary and secondary care and apply algorithmic analysis of electronic health records, genetic profiling, family history, data on individual lifestyle, diet, behaviour and occupational health, as well as environmental information to deliver a dynamic cancer risk scale for each patient throughout their life. Some of this data could be harnessed from devices such as mobile phones, wearables, and other sensors from the consumer industry. This dynamic risk scale would evolve as the patient's circumstances change and track risk from birth throughout a patient's life and thus enable identification of high-risk individuals before the onset or at the early onset of symptoms. While there remain logistical challenges around the aggregation of data from a plethora of heterogeneous systems, the creation of such a "smart" cancer risk scale, would facilitate a more accurate early identification of high-risk individuals, which can save lives as well as costs.

Although several clinical decision algorithms and tools exist to support GP decision making, such as QCancer®[10] and other tools[11,12], these are woefully underused. Doctors interviewed by Health Enterprise East (HEE) deplored the poor design of the user interface of many of these tools and the lack of cross-platform compatibility as well as the need for manual data input. Significant scope for improvement appears to exist in the design of a more intuitive clinician dashboard which should work easily within the setting of a 10-minute consultation. Some novel digital platforms designed to catch cancer earlier in primary care, such as C the Signs[13] have shown significant improvements in and cancer staging, reduction in emergency presentations and improvement in staff efficiencies[14, 15].

Genetic testing as a part of a future diagnosis and treatment strategy

Characterisation of patients' genetic profile is expected to play a major part in future cancer care as part of a more personalised approach to early cancer detection and diagnosis. Variant Breast Cancer genes BRCA1 and BRCA2, for example, increase a patient's likelihood of developing breast cancer and act as an early indicator of a high-risk individual. Other genetic indicators of cancer susceptibility are expected to be discovered in the future as our understanding of the human genome deepens.

Genetic testing will also play an important role in the emerging market for immuno-oncology and cancer treatment which are highly effective in patients with a specific genotype, such as angiogenesis inhibitors for non-small-cell lung cancers (NSCLCs) with certain EGFR mutations.

Diagnostic accuracy trade-offs

Once a high-risk individual has been identified, early diagnostic testing can take place. At this stage, a delicate balance needs to be struck between diagnostic accuracy and cost.

Diagnostic accuracy is expressed as sensitivity and specificity; sensitivity is the ratio of true positives to the total number of diseased individuals in the population whereas specificity is the ratio of true negatives to the total number of healthy individuals in a population. (*Figure 6)*

$$\text{Sensitivity} = \frac{true\ positives}{true\ positives + false\ negatives} = \frac{number\ of\ true\ positives}{total\ number\ of\ diseased\ individuals\ in\ the\ population}$$

$$\text{Specificity} = \frac{true\ negatives}{true\ negatives + false\ positives} = \frac{number\ of\ true\ negatives}{total\ number\ of\ healthy\ individuals\ in\ the\ population}$$

	Diseased	Healthy	
Positive test	True Positives	False Positives	**Total Positive**
Negative Test	False Negatives	True Negatives	**Total Negatives**
	Total Diseased	**Total Healthy**	

Figure 6 - Measures of diagnostic Accuracy

An expensive but very accurate test would add a significant cost burden on the healthcare system, whereas a cheap test with lower accuracy would create a multitude of other problems;

- If test sensitivity is too low, the test will produce a high proportion of false negatives. These cancers will then progress to develop into more advanced cancers and negate the purpose of an early detection and diagnosis strategy
- If test specificity is too low, the test will produce a high proportion of false positives. These falsely diagnosed cancers will be treated and monitored, significant cost to the healthcare system and endanger the cost-effectiveness of the testing programme

Typically, early-stage screening tests aim to have a higher sensitivity whereas tests employed later in the diagnostic pathway aim to major on specificity.

Optimal positioning of diagnostic technologies

This specificity/sensitivity trade-off will determine the optimal positioning of a diagnostic technology on the diagnostic pathway. Innovators and medical technology companies developing diagnostic technologies for use in cancer need to gain a thorough understanding of the current diagnostic pathways in the markets targeted as well as the diagnostic accuracy of their technology to ensure ideal positioning to delivering maximum benefits for the price charged.

Cost-effectiveness of early diagnosis is likely to differ with the type of cancer as well as the effectiveness of the treatment options available.

Early diagnosis of some cancers risks the detection of a large proportion of non-clinically significant cancers; cancers which would not cause the patient any problems within his or her lifetime. For example, screening programmes done in prostate cancer and breast cancer led to a large proportion of non-significant, slow-growing cancers being detected[16,17]. As it is not always possible to distinguish a clinically significant from a non-significant cancer *a priori,* tumours which are detected need to be monitored and treated, leading to additional cost burden on the healthcare system from monitoring and over-treatment of tumours with low malignant potential. An overly high proportion of non-clinically significant cancers can thus prove to be detrimental to the relative cost-effectiveness of a diagnostic technology by increasing the overall cost of managing the condition while decreasing the impact on health outcomes[18].

However, diagnosis of clinically significant cancers is but one part of the equation; cost-effectiveness of a diagnostic technology depends on the decisions it informs. If the treatment options available do not have a sizeable impact on quality and length of life, there are limits to how much a diagnostic can impact health outcomes.

The challenges posed by Covid-19

One cannot ignore the vast disruption to cancer diagnosis caused by Covid-19. The hybrid system of screening and early diagnosis in the UK has been thrown into disarray by the Covid-19 pandemic. Cancer screening was suspended in March 2020, and individuals who may otherwise have sought out a primary care physician over symptoms they worry about, are now staying at home and avoid interaction with doctors[19]. At the same time, the UK National Health Services (NHS) has focused most of its energy on the care for patients with Covid-19, delaying and cancelling other consultations and interventions. As a result, referrals to secondary care diagnostic services have plummeted by up to 84%[20]. This is forecast to result in additional deaths directly attributable to the lockdown, as well as due to the backlog of uninvestigated patients. As an easing of restrictions may not be on the cards this year, we are looking at a sizeable backlog in 2021. In-hospital diagnostic tests such as endoscopies and imaging may only be performed for patients classified as high-risk due, and so a higher proportion of late-stage cancers is likely to be diagnosed.

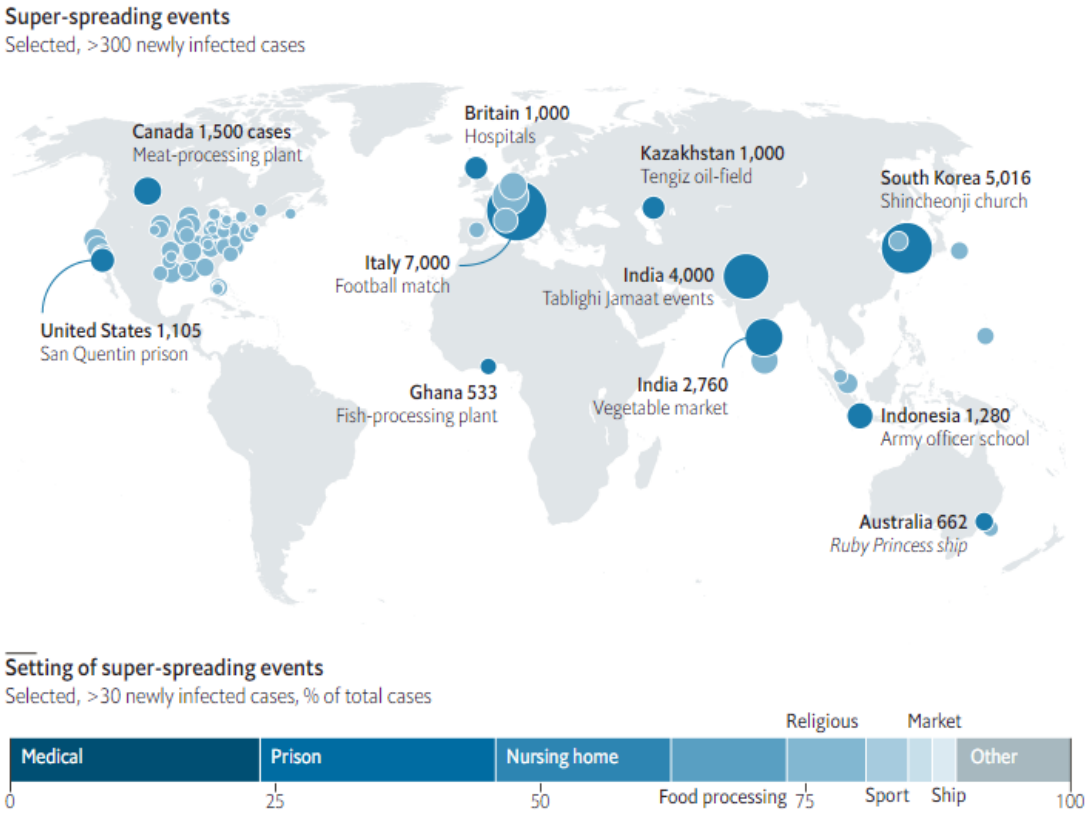

Figure 7 - Share of covid infections caused by super-spreader events - © The Economist Group Limited, London (Nov '20)

Since most UK super-spreader events in the first wave have originated in hospitals (see *Figure 7*), a delicate balance needs to be struck between minimising the risk of infection to patients and the need for diagnosis and treatment of cancerous tumours, otherwise, the wave to covid-19 mortality will be followed by a tsunami of premature cancer deaths.

The diagnostic capacity of the UK has long been lagging that of other European nations[21], and the NHS Long Term Plan sets out ambitious goals for modernising and expanding the national diagnostic capacity for cancer[22]. This need has become urgent during the pandemic and the repurposing of the Nightingale hospitals to cancer testing centres[23] is expected to spawn new diagnostic pathways to manage the significant backlog. Telemedicine, computational intelligence methods[24] and use of improved triaging tools across primary and secondary care are expected to be part of expedited cancer diagnostic pathways in pandemic times and beyond.

What does the future hold?

The future of cancer care will be dominated by preventing the condition rather than treating it. Early identification of high-risk individuals by harnessing the rich ecosystem of data we are all increasingly living in, will be key to this strategy. Genomic profiling, computational analysis of large data sets (Artificial Intelligence (AI)) combined with micro-targeting of advice given to high-risk individuals based on their risk profile and life circumstances, is expected to play a significant part in lowering the incidence of cancer in the future.

As our treatment options for cancer improve, managing the disease will be akin to managing a chronic condition such as diabetes. This requires monitoring and long-term surveillance of the progression of the disease in a cost-effective way, which could be done by the patient as well as the

healthcare professional[25]. Easy-to-use technologies for monitoring cancer progression, which enable patients and their families to participate in managing their care by combining monitoring with personalised advice will be important pillar stones of future cancer care strategies. Liquid biopsy testing holds a lot of promise for future cancer care management[26] as it allows the minimally invasive diagnosis and tracking of tumour development by testing tumour-specific biomarkers in a sample fluid such as blood, plasma, saliva, urine, seminal fluid and others. Notable examples include the liquid biopsy test being developed for prostate cancer by Cambridge Oncometrix[27] , for lung Cancer by Oncimmune[28], and the multi-cancer liquid biopsy technology developed by Grail Inc, which uses longitudinal analysis for detection and monitoring of several different types of cancers[29]. A noteworthy diagnostic modality in this space is Breath Biopsy®, currently in development by Owlstone Medical, which aims to detect biomarkers in respiratory droplets and volatile organic compounds (VOC) indicative of the disease stage[30]. Though many of these technologies are still based in laboratories, point-of-care or even at-home monitoring tests are expected to play an increasingly important role in the future.

These diagnostic and monitoring technologies of the future need to balance cost and accuracy by ensuring optimal positioning within the cancer care pathway, and lead to improved decisions by healthcare providers as to the type of advice and/or therapeutic treatment to provide. Ultimately, we must not forget that it is not the diagnostic technology which improves a patient's length and quality of life; but the decisions ensuing from it.

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