Screening for Disease and Risk of Disease:

Present and Future Considerations, Caveats and Consequences

RGA

Contents

Screening: The Fundamentals

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Introduction

Early detection of disease in apparently healthy individuals has an intuitive appeal arising from the notion that early diagnosis is synonymous with cure. Screening originated as a medical strategy for the purposes of identifying occult disease in individuals before the development of symptoms and signs. The enthusiasm with which screening was adopted was based on the idea that the deployment of treatment strategies at a preclinical stage would limit advanced disease and reduce mortality.

With time, the scope of screening has broadened to include the identification of those at an increased risk of disease and has come to encompass the collection of genetic data for that purpose.

Screening is no longer confined to the field of medical practice, where it is undertaken selectively in accordance with an individual's clinical risk profile, and where there are proven opportunities to improve health outcomes. Screening is now undertaken outside of clinical settings by various service providers and potentially improperly promoted. Testing is commonly driven by poorly informed consumer demand and often incorrectly targeted without due regard for the predictive value and the consequences of the findings.

The data gathered, even when collected with informed consent, may not be owned by the individual and may be used by providers in ways that are not open to the consumer or capable of scrutiny. The utility of screen-detected findings, particularly if deployed indiscriminately outside of evidence-based mainstream settings, needs to be interpreted by trained professionals with an understanding of the performance characteristics of the test within the environment in which it was applied.

The mere availability of screening techniques does not imply that testing should be broadly applied without a considered focus although the current environment is such that this is increasingly the case.

Screening outcomes become powerful determinants of costly medical interventions and are important drivers of decisions taken outside of clinical medicine on behalf of people not seeking medical help.

Inappropriate screening may harm healthy individuals, squander resources, trigger extensive reflex testing and result in unintended outcomes. While ever more sensitive screening modalities generate important data regarding the true burden of disease, the ramifications are not necessarily advantageous.

Genomic screening, particularly when undertaken in a non-targeted fashion without a clearly defined intent, has introduced a new layer of extreme complexity to the screening environment. The interpretation and application of broad-based genetic data requires considerable expertise which includes an understanding of gene expression and penetrance. It needs to be

recognised that there are many influences which come to bear on the development of a phenotype, or the manifestation of disease, in those who might be genetically predisposed.

From an insurance perspective, screening test results need to be managed carefully with due consideration of the context in which the test was undertaken and with a clear understanding of the degree to which the results can be validly applied to the individual being assessed.

Identifying conditions that are known to be highly prevalent in the applicant population, and which are already accommodated in premium structures, can lead to prejudicial decisions that are overly conservative.

Findings that identify a risk for some future health event need to be interpreted and managed with respect to the degree to which any lag time might exist before there is any insurance impact.

This paper will focus on early disease detection, and not on predictive testing or genetic screening, although the application of genetic information for insurance purposes, where permitted by law, is coming to the fore and increasingly the province of those with specialized training and expertise.

Screening for Disease

Screening for disease refers to the application of a test in populations with no signs or symptoms of disease with the aim of detecting the targeted condition and treating that condition before it becomes clinically evident.

These tests were developed for clinical purposes and are not diagnostic in themselves. They are investigations that identify individuals who require further evaluation in order to rule in (confirm) or rule out (exclude) the condition in question.

Despite the notion that early detection provides an opportunity for curative intervention, it cannot be assumed that all those with a screen-detected abnormality will benefit from that early diagnosis.

Medically accepted screening programs are governed by ethical imperatives that require evidence that the benefits outweigh any harm and proof that outcomes are advantageous and not disadvantageous to the individual. Indiscriminate screening, driven by consumer demand, nonmedical forces and commercial interests, may not always see those boundaries respected.

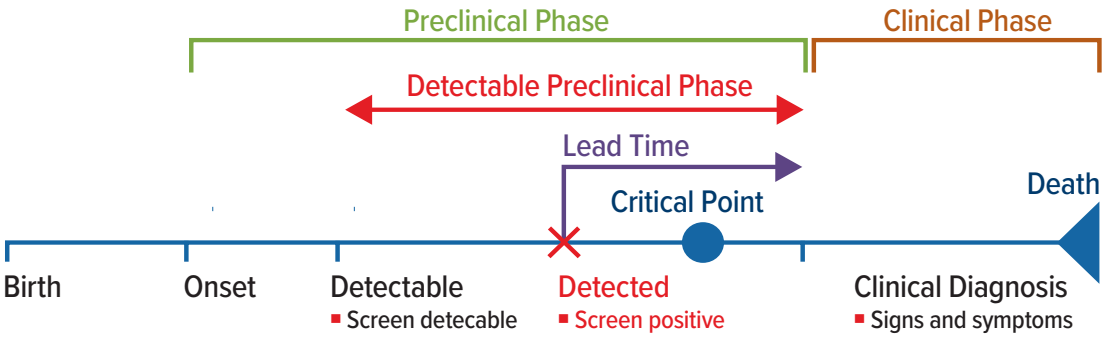
Understanding Screening Test Performance

Screening can only be justified if a test, applied during the preclinical phase of a disease, has the potential to positively influence the outcome.

The time from a screen-detected diagnosis to the time a clinical diagnosis would otherwise have been made is called the lead time. The test becomes useful when a preclinical diagnosis is able to be made before a critical therapeutic point is reached. The critical therapeutic point is the point after which treatments do not influence the outcome of a screen-detected condition (Fig 1).

Survival improvements that appear to be a consequence of a screening diagnosis can be more illusory than real and must be interpreted in the context of disease behavior. An apparent survival advantage after a screen detected diagnosis should not necessarily be interpreted as proof that an early diagnosis leads to a benefit.

Figure 1



An ideal screening test would accurately and reliably discriminate between those with, and those without, a condition.

A perfect test would have the capacity to identify the condition in all those with that condition and would miss no cases. All those with the condition would test positive and there would be no false negatives. That test would be deemed to have a sensitivity of 100%.

Also, a perfect test would have the potential to correctly identify all those who do not have the condition and not detect any abnormality in healthy individuals. All those without the condition would test negative and there would be no false positives. Such a test would be deemed to have a specificity of 100%.

Unfortunately, no screening test has perfect precision.

Imperfect sensitivity results in conditions being missed (false negatives) and imperfect specificity results in individuals without the condition being incorrectly labelled as having that condition (false positives).

The pursuit of full sensitivity, driven by the quest to miss no cases, is usually associated with a loss of specificity that exposes some individuals to unnecessary investigations and the associated hazards and costs.

When determining the value and applicability of any particular screening modality consideration must be given to the degree to which there is any tradeoff between sensitivity and specificity.

What is considered acceptable will depend on the implications of missing a crucial diagnosis when judged against the implications of mislabeling and overdiagnosis.

While increasing test sensitivity has resulted in the capacity to identify the true prevalence of disease it has resulted in the diagnosis of some conditions that might never have led to any adverse health consequence during the insured's lifetime. This is referred to as overdiagnosis and leads to unnecessary treatment and anxiety.

Both incorrect labelling and overdiagnosis have important insurance consequences with increased exposure to lump sum living benefits and health costs.

From an insurance perspective the interpretation of a screening test result ultimately comes down to its predictive value.

The predictive value of a test expresses the degree to which a result can be relied upon to have correctly determined the status of the individual.

The positive predictive value (PPV) is the degree to which a positive test can be relied upon to have correctly labelled an individual with a condition and the negative predictive value (NPV) is the degree to which a negative test has correctly labelled an individual without the condition. It is expressed as a percentage and is calculated from the tests capacity to result in true and false positives and true and false negatives.

No conclusion can be drawn on the implications of results without knowing the probability of the condition being present in the population being tested. This notion is expressed in the Bayesian probability theory which states that the probability of a test result providing valid information requires a consideration of how likely any given person is to have a disease in the first place (the pretest probability) and the sensitivity and specificity of the screening tool.

If the prevalence of a disease in a population or an individual is low, it is inevitable that there will be more false positive results than true positive results and the test will have little predictive value. The predictive value of a positive test approaches zero if the population screened is essentially free of the condition in question.

A positive test result is likely to be a true positive (correctly identifying the presence of the disease) if deployed in populations or individuals with a high chance of having the disorder. A positive test result is likely to be a false positive if deployed in an individual with a very low chance of having the condition.

Similarly, the validity of negative tests must be questioned if they do not fit the predetermined pretest likelihood of disease.

While screening for certain conditions in appropriately targeted populations carries a recognised advantage there are many considerations which need to be examined when assessing the value of protocols.

Proof of effectiveness of a screening tool is best confirmed by a demonstrable effect on mortality. Other measures of effectiveness are often quoted and have pitfalls which have the potential to introduce bias.

Understanding Bias

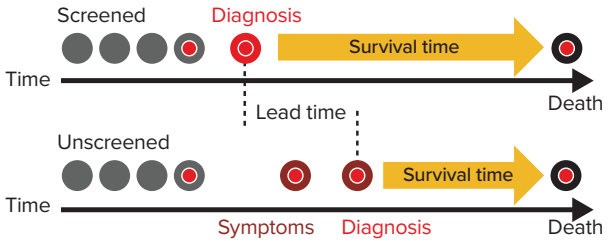
There are a number of biases that need to be understood when assessing the merits of screening protocols; these include lead time bias, length time bias, and overdiagnosis bias.

1. Lead time bias

Lead time bias refers to diagnoses which result in an improved survival time following a diagnosis while not influencing the actual time of death. Although the period of time to death differs by mode of diagnosis (screened vs. unscreened), the time of death may not have been influenced (Fig. 2).

Lead time bias creates a false impression that an early diagnosis has produced a benefit, whereas screening might only have resulted in a longer survival time after diagnosis than might otherwise have been the case.

Figure 2



2. Length time bias

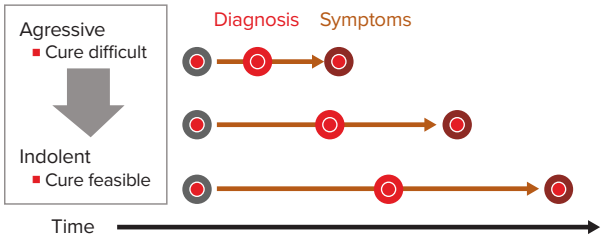
Length time bias refers to the fact that the probability of screen detection is related to the speed of disease development and progression.

Very fast-growing cancers have a short window between the potential for detection by screening and the development of symptoms. These cancers may develop and progress rapidly to a prognostically disadvantageous stage between traditional screening intervals. In these situations screening may be deemed to be ineffective at identifying early disease and in modifying the prognosis.

Slow-growing indolent cancers of the same organ are more likely to be screen-detectable because the asymptomatic phase is protracted. Screening will be deemed to have produced a benefit by way of early diagnosis and the apparent value enhanced by that fact that the tumor, by its very nature, is easily cured (Fig. 3).

Persons with slowly progressive disease will be overrepresented in cohorts and their survival will be naturally longer. The longer survival may be wrongly attributed to early detection and therapy.

Figure 3



3. Overdiagnosis bias

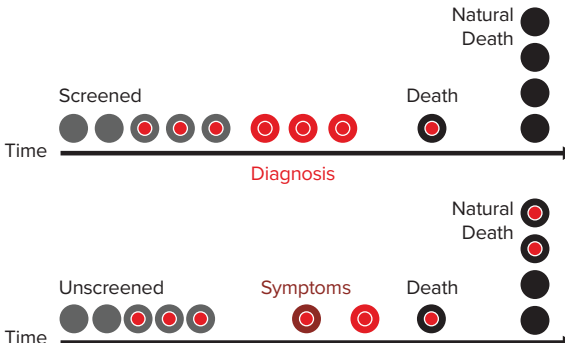
Overdiagnosis bias is an extreme of length time bias.

This refers to the screening diagnosis of indolent disease that would not have caused excess mortality had it never been diagnosed in the first place (Fig. 4).

Treatment results in an apparent survival improvement in the screened population and can be improperly interpreted as evidential support for testing. Outcomes should be adjusted for overdiagnosis bias before any screening program is deemed useful.

Overdiagnosis, or the identification of pseudo-disease, leads to unwarranted anxieties and adverse treatment related outcomes. Overdiagnosis and over treatment increases critical illness and disability exposure and may actually increase all-cause mortality.

Figure 4



Population screening takeaways

Population screening for disease is only defensible where:

1. The disease is prevalent.
2. The disease has serious consequences.
3. The preclinical phase is long enough to permit a reasonable testing frequency.
4. There is a capacity to detect disease before the critical therapeutic point is reached.
5. The test has a high detection potential (good sensitivity).
6. Testing detects little irrelevant disease (good specificity).
7. The overdiagnosis rate and the consequences of overdiagnosis are acceptable.
8. The test carries an acceptable risk without significant morbidity.
9. Effective treatment for the disease is available.
10. The treatment is more effective if administered in the preclinical phase.

Bias or Benefit

While the protective value and health benefits of properly directed screening programs are not in question, overdiagnosis and overtreatment have become an unavoidable consequence of ever more sensitive screening modalities.

The adverse outcomes of screening healthy individuals have become increasingly important and the cost, stigma, and potential injury associated with screening outcomes must not be ignored in the quest for earlier diagnoses. This has become particularly evident in the overdiagnosis associated with screening for cancer.

Mitigation of the potential adverse outcomes of screening and the avoidance of mislabeling and overtreatment will likely come in the guise of an increased understanding of disease behavior and an enhanced capacity to abandon the “one size fits all” therapeutic approach that currently follows many early diagnoses.

A better understanding of diagnostic outcomes and changes in disease labelling, driven by genetic determinants and other disease mediators, will be central to solving that concern.

Applying Screening in the Insured Population

While benefits for screening certainly exist, a proper understanding of the pitfalls and challenges of disease screening is crucial to the application of screening protocols in insurance medicine.

Screening in one form or another will remain part of risk selection if anti-selection is to be avoided and if the cross subsidization of substandard applicants by healthy populations is to be minimized.

Individuals who see themselves as healthy and risk averse might reasonably expect assessments to take their individual circumstances into account with a view to maximizing the benefits of healthy lifestyle choices and minimizing premium imposes.

An increasing focus on individual risk stratification has many implications including pricing imperatives within otherwise broadly aggregated pools.

Maximizing the utility of screening for insurance purposes will require the industry to select and deploy meaningful tools which have an acceptable degree of precision and which are not considered to be overly intrusive by applicants. It will also require the industry to acquire a knowledge base that allows the results of screening tests, undertaken outside of the underwriting process and disclosed at application, to be applied accurately and with fairness.

There will inevitably be a need to carefully consider trade-offs.

Generally speaking, screening will continue to focus on predictive modelling at the younger ages (where even high risk parameters have had no time to be expressed as a phenotype) but perhaps move more to a disease prevalence screening model at the older ages if we are to assess applicants more as individuals.

Screening for phenotypic expression has the potential to modify traditional risk-factor based underwriting but integrating multiparametric models requires a considerable understanding of disease behavior and a determination of how these models interact and integrate.

Are the Winds of Change Blowing?
An examination of the developing tools for screening and diagnosing Alzheimer's Disease

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Introduction

Alzheimer's Disease (AD) is the most common form of dementia accounting for 60% to 80% of the total cases, which is estimated at 55 million worldwide. About 75% of people with dementia may be undiagnosed; this figure may be as high as 90% in low- and middle-income countries.[1] Yet, there is still no consensus among the major guidelines on population-based screening in elderly communities.

Societal and self-stigma around AD and dementia are barriers to diagnosis of AD; paradoxically, this is compounded by a common misconception that dementia is part of normal aging.[1] Currently, AD screening is typically triggered by reported symptoms and is only a preliminary step in the AD detection process. Screening is followed by either further monitoring over time or a complex diagnostic process that is often costly and typically punctuated by much time delay, making AD diagnosis a protracted, costly task to undertake.

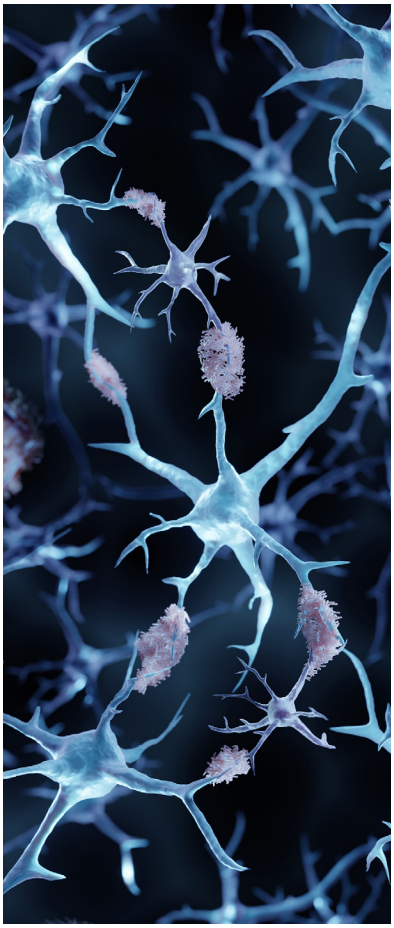
From the clinicians' perspective, many challenges also exist as highlighted by the 2021 World Alzheimer's Report.[1] The problems include: the perception that currently available interventions offered low clinical value rendering the diagnostic process futile; the lack of access to specialized diagnostic tests in the primary care setting; and the need for tests that improve AD diagnostic precision.

Recent pharmaceutical advances have ignited the hope for effective disease modifying treatments for AD that may alter its management and clinical trajectory. In addition, developments in AD biomarkers evaluation over recent years are causing a major shift toward a biologically based diagnostic approach, which may enhance AD detection accuracy. Biomarkers are measurable laboratory or imaging tests marking specific disease pathologies.

Clinical use of AD biomarkers, such as imaging scans and cerebral spinal fluid (CSF) protein assays, have been well established at least in research settings and incorporated into diagnostic guidelines from 2018. Biomarkers such as CSF amyloid-beta and tau proteins have often been used to identify AD candidates for interventional trials that target such pathologies. These have not been widely adopted in primary care settings due to the cost of neuroimaging, lack of clinical expertise outside of specialist centers, and the invasiveness of obtaining CSF samples.

This article's focus is looking at the newer biomarkers being developed and asks the following question:

1. How would ongoing developments influence the current AD screening and diagnosis framework?
2. What are the downstream implications for the insurance industry amid an aging world population?



Background Medical Information

Alzheimer's Disease is a spectrum of disease manifestations potentially spanning decades

The spectrum of neurological decline in AD begins with preclinical changes that may be present up to 20 years before the onset of clinical dementia, transitioning past the state of mild cognitive decline of MCI, which may precede overt dementia by 10 years. MCI, by definition is a state of cognitive impairment that is evident in neurocognitive assessments but has not yet impacted the activities of daily functioning. Much of the neuropathological changes found in Alzheimer's Disease may also be present to a lesser degree in MCI. These include amyloid accumulation, synaptic dysfunction, tau-mediated neuronal injury and brain volumetric loss.[2]

Early symptomatic AD is in fact equivalent to advanced stages of molecular pathology; this opens up to the potential of earlier detection of AD.

Alzheimer's Disease is a complex disease with multifactorial pathogenic elements.

The main pathologies in AD are neuronal injury, synaptic dysfunction, and neurodegeneration that lead to cognitive, behavioral, and functional deterioration. Two established hallmarks of AD are extracellular amyloid-beta (Aβ) aggregation and intracellular hyper-phosphorylation of tau protein accumulation, possibly representing late processes in this disease's pathogenesis.[3] Molecular processes that have been implicated as contributors toward the earlier pathogenesis of AD are inflammation, immune dysregulation, vascular injury, oxidative stress, mitochondrial dysfunction, and calcium-mediated toxicity.

AD is a multifactorial disease resulting from complex multi-directional interactions between various pathogenic factors that results in a highly heterogeneous disease that manifests differently from individual to individual.

Only about 25% of AD cases are familial and about 5% are known hereditary early-onset disease that are associated with identified mutations, namely APP, PSEN1 and PSEN2 that are located on chromosomes 21, 14 and 1, respectively. They may contribute toward abnormal Aβ production or clearance. The APOE e4 allele is a known genetic risk factor for late-onset Alzheimer's dementia, but its correlation is highly variable. Autosomal dominant inheritance of PSEN mutations can lead to early onset AD. Other genetic risk factors are continually being uncovered.[4]

These biological factors add to social factors that form complex and challenging hurdles in the screening and diagnosis of AD.

The Challenges in Screening and Diagnosing AD

The current clinical process of detecting and diagnosing AD dementia, MCI, may not offer a high degree of certainty in risk assessment during underwriting and claims processes.

For most of the last decade, the clinical diagnosis of AD was one of probability based mostly on a clinical syndrome of dementia. Without histopathological confirmation obtained by biopsy or autopsy, the diagnosis was either probable or possible AD depending on various clinical features added to the findings of cognitive testing.[5] The Diagnostic and Statistical Manual (DSM) diagnostic approach is still mostly a clinical one using neuropsychological evaluations.[6] Cognitive testing tools such as the Mini Mental State Examination (MMSE) or mini-cog that are used as screening tools for dementia have variable accuracies, with the abilities to detect and to rule-out dementia in primary care settings estimated at around mid-70%.[7] This may be further reduced due to language or cultural factors in some environments. Furthermore, the agreement of clinical diagnosis of AD (without biomarkers) to post-mortem histopathological confirmation of AD ranges from 50% to 80%.[8,9]

Consequently, the diagnosis of dementia has often required follow up monitoring with repeated cognitive and neuropsychiatric evaluation to improve the accuracy of diagnosis. Furthermore, the clinical diagnosis of AD dementia may have low correlation to the definitive pathological diagnosis. Prior to the introduction of imaging or cerebrospinal fluid biomarkers, the median sensitivity and specificity of clinical diagnostic methods for Alzheimer's Disease dementia even at AD centers were 87% and 58%, respectively.[10]

When biomarkers were introduced into diagnostic guidelines in 2018, it signaled a move toward a biological model that also indicated an ability to correlate certain biomarkers to different stages of the clinical AD continuum of preclinical, MCI, and dementia stages.[5] The earliest utilized biomarkers were neuroimaging and CSF protein levels. They may have improved accuracy and confidence in the diagnosis but have also led to a process that is complex, costly, and invasive.[11]

Much of the current research is looking to finding more accessible and less costly diagnostic assays, with some showing much more utility and promise.[12,13]

Please see pages 10 - 11 for a quick review of current AD diagnostic pathway.

An in-depth look to compare CSF biomarkers and novel fluid biomarkers in evaluating AD

CSF and plasma biomarkers function well as markers of the defining pathological hallmarks in AD which are amyloid plaques, neurofibrillary tangles, and neurodegeneration. Some may be detected before clinical manifestation. They can also be repeated over time to track progression.

CSF Biomarkers

As amyloid-beta peptides aggregate in brain tissues, they form fibrils and plaques that lead to brain tissue inflammation and death of neurons. Tau proteins are found in axons and play important roles in regulating certain functions inside the axons. The hyper-phosphorylation (addition of phosphates molecules) of Tau protein makes them insoluble, leading to aggregations creating neurofibrillary tangles (NFTs) inside the axons causing axonal dysfunction. In AD, CSF Aβ levels drop, and CSF Tau levels rise.

Measurements of CSF amyloid-beta (Aβ) levels began in the 1990s. As Aβ42, the form that is most prone to aggregation, accumulates in brain tissues, its CSF level drops correspondingly, which can be measured by various methods. These changes correlate well with findings on amyloid PET scans; the accuracy is improved further by using the ratio of Aβ42 to Aβ40 which reduces the impact of inter-individual variations.[14, 15]

Raised CSF phosphorylated tau (p-tau) proteins can be measured reliably. In addition to total tau levels, different p-tau subgroups (named according to the location of the phosphorylation) can be measured; significant ones include p-tau 181, p-tau 217, and p-tau 231. They may perform differently: some correlate better with PET scan findings, some may track longitudinal changes better, and some may strengthen the differentiation of AD from other dementias.[16, 17]

What is the current clinical pathway in detecting and diagnosing AD?

The screening process of AD is typically triggered by a perception of cognitive decline. Much of the initial process is reliant on deriving subjective or collateral conclusions from each patient's history and relying on observations shared by a family member or a caretaker. Current guidelines do not advocate for screening asymptomatic elderly individuals.[14, 15]

Key elements used in the evaluation of suspected AD vary by region and are resource dependent.[14, 15]

1. **Reported history**

   This entails an account of the level of functioning, including activities of daily living (ADLs). An enquiry of possible risk factors may identify reversible causes of cognitive decline (CD) as well as family history of dementia and neurodegenerative disorders. Corroboration by collateral history is required.

   Drawback: Highly subjective.

2. **Physical examination and laboratory investigations**

   These include blood, urine tests, ECG, X-ray, full physical examination, psychiatric assessment, and investigations to identify any potentially reversible causes. Physical exams also assess for dementia mimickers such as delirium, depression, drug reactions, sensory impairment such as hearing or vision loss, and for co-existing disorders.

3. **Cognitive testing**

   Typically, these test memory, problem solving, attention, counting, and language. There are many in use. Examples include the Mini Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCa), St. Louis University Mental Status Examination (SLUMS), the 10-points cognitive screener, and the six-item cognitive impairment tests, to name a few.

   Note: These are screening tests to detect cognitive impairment. They may be repeated over time to track progress and changes. They may need additional correlation by other clinical assessments such as neuropsychological, neuropsychiatric, or neuroimaging tests depending on the clinical context.

   Drawback: May be impacted by cultural background, education levels, and language capabilities of the test subjects. Some have been developed for a specific population group such as the Kimberley Indigenous Cognitive Assessment (KICA-cog) for use in the remote indigenous Australian population.

4. Imaging biomarkers[15,18]

Most guidelines recommend various imaging modalities depending on the history and clinical assessment. Both structural and functional assessments using computed tomography (CT) scan or magnetic resonance imaging (MRI) are utilized. These modalities may not be available in all clinical settings depending on resources.

Structural imaging, such as a brain CT scan, can demonstrate atrophy and previous stroke, as well as detect tumors or possibly reversible causes of dementia symptoms. MRI can assess brain structure, size, chemistry, vascular flow, and function; this may help with distinguishing different causes of dementia.

Functional scans such as FDG PET (F-flurodeoxyglucose-positron emission tomography) can demonstrate reduced neural activity as a marker of neural injury before structural abnormality are detectable. It has been shown to raise the diagnostic accuracy of AD significantly. Single photon emission tomography (SPECT) is useful in assessing brain cell activities as a measure of functionality.

Intracerebral lesions of both amyloid and tau proteins can be measured on positron emission tomography (PET) scans by using FDA-approved tracers. Amyloid accumulations detected on PET can be highly predictive for AD in the 60 years or younger group, whereas a negative amyloid PET is useful in ruling out AD. Similarly, Tau PET scans can detect abnormal aggregations of tau protein associated with neurofibrillary tangles and have been shown to track disease progression.

Drawback: High-cost, radiation exposure, and may be only available at specialist centers.

5. Fluid biomarkers used in AD[15, 18]

Protein biomarkers in cerebral spinal fluid (CSF) have long had an established role as supportive diagnostic tools in AD research. Several proteins have demonstrated good sensitivity and specificity. Those already in significant use are total Tau (t-tau), phosphorylated-tau (p-tau), amyloid-beta 42 (Aβ 42), and amyloid-beta 40 (Aβ 40).[17] They are markers of the core pathological processes in AD. Adoption in clinical medicine has been slow due to required invasiveness, and these evaluations are still mostly available in specialist settings only.

6. Genetic markers

Genetic testing is not routinely used in the evaluation of possible AD but is relevant in those with strong family history involving multiple members, especially those with early-onset disease or where there is a pattern of autosomal dominant inheritance.

Many other CSF biomarkers have shown promising function as AD markers, including beta site-amyloid precursor protein (APP)-cleaving enzymes 1 (BACE-1), synaptic dysfunction or injury markers such as Ng, SNAP25, and Sut1, to name only a few. There are ongoing evaluations to investigate their suitability and performance as AD markers.

In recent years, much development in the technical aspects of these assays brought improvements in standardization and pre-analytical handling that led to more clinical use in specialist centers outside of research environments, in some parts of the world.

Plasma Biomarkers

Aβ and Tau proteins occur at much lower levels in blood as compared with CSF levels. Advancements in measuring plasma levels of these pathological AD markers were made possible only after development of ultra-sensitive technologies that were able to detect much lower levels.

Significant breakthroughs include the demonstration of a correlation between blood level p-tau 181 with its CSF level and amyloid PET findings. Abnormalities are detectable in the years preceding clinical presentation, thus positioning blood level p-tau 181 as a marker of AD pathology with potential to stage the AD clinical course. In addition to identifying AD, blood level P-tau 217 may differentiate AD from other dementias more effectively than brain MRI, blood level p-181, and blood level of NFTs. Abnormal levels are also detectable before PET scan changes and onset of clinical symptoms.

Similarly, plasma levels of Aβ42/40 ratio showed good accuracy when measured against CSF level ratios and amyloid PET scan findings with some suggestion of the ability to predict progression of cognitive decline.

Blood levels of neurofilament light chain (NFL), an axonal component, can be measured using Single Molecular Array (SIMOA) and have been found to correlate well with brain atrophy in AD. When looked at together with Aβ abnormalities, NFL detection is associated strongly with mild cognitive impairment.

Not surprisingly, many other proteins involved in neuronal and synaptic injuries, neuro-inflammation, and immune dysregulation have also been identified as potential candidate biomarkers of dementia and possibly other neurodegenerative disorders. In fact, these markers reflect the important molecular pathways or cellular abnormalities occurring in different stages of AD and dementia. Much effort continues to be devoted to looking at non-invasive biomarkers in saliva, urine, nails, and hair to find more accessible assays; there is no reported success as yet.[16, 18] Investigations of some of these biomarkers may help to elucidate pathological processes that can become targets of therapy and intervention research.[3]

The Synergistic Power of Combining Multiple Biomarkers

In the research field, there is much interest in investigating easily obtainable biomarkers for AD detection across its full clinical spectrum, as well as possible predictors of cognitive decline.

Many biomarkers are indicators of AD pathology even in the pre-symptomatic stages. A recent breakthrough came from University of Hong Kong, where a research team developed a 19-plasma-protein panel that detected AD with 97% accuracy in a small research sample group. It also allowed differentiation of severity stages with an accuracy that is superior to the other known biomarkers.[19] Such early success now needs to be replicated in larger studies. This study, in fact, follows previous protein panels developed by other institutions that unfortunately could not be validated by additional research.

Other researchers are exploring the ability to combine cognitive testing with blood tests of plasma biomarkers and genetic markers with the objective of establishing a risk score predicting progression in cognitive decline. Early results from this investigation appear promising.[20, 21] However, validation in a much wider and diverse population is required.

The Winds of Change are Blowing

There are promising developments in peripheral biomarkers that have shown strong potential as markers of AD pathologies and possibly the ability to demarcate different clinical stages of the AD disease spectrum. The long silent prodromal stage of AD

offers an ideal window for screening, particularly if reliable, non-invasively obtainable biomarkers become available and if effective treatments targeting early pathological processes are developed. Further work is required to establish where along this clinical spectrum detection would offer the most clinical value.

Novel biomarkers could even aid clinicians in differentiating AD from other dementia-causing diseases. Some of these plasma marker assays have already received technical approval for clinical deployment. Many more are undergoing validation studies to assess their diagnostic performance. The addition of molecular and structural neuroimaging would further supplement the diagnostic accuracy of biomarker screening, especially in cases with complex presentation.

Blood-based biomarkers would lower many of the barriers of AD detection in primary care settings, particularly with consideration of cost and invasiveness. This can potentially help make the detection of early AD or prediction of AD progression a reality, even in primary care. In addition, blood-base biomarkers may provide a tool for population-based AD screening. However, other barriers to screening and diagnosis of AD, such as social stigma and access to health care facilities would also need to be addressed.

Such trends may improve the certainty of AD dementia diagnosis, which can assist underwriters and claims administrators. At the same time, it potentially will increase AD incidence and prevalence globally, including early stage AD, which only has a minimal negative impact on affected individuals. Future insurance product design must be cognizant of these evolving trends.

The confluence of a global aging population, improving biological diagnostics, and the availability of future disease modifying treatments, is likely to trigger a material increase in AD incidence globally. Many countries, especially those with aging populations, have been putting in place infrastructure to offer community and in-patient support to affected individuals and their families throughout the various clinical stages of the AD disease spectrum and other forms of dementias. An appropriate insurance product may lend much needed support.

Cancer Screening – The Status Quo

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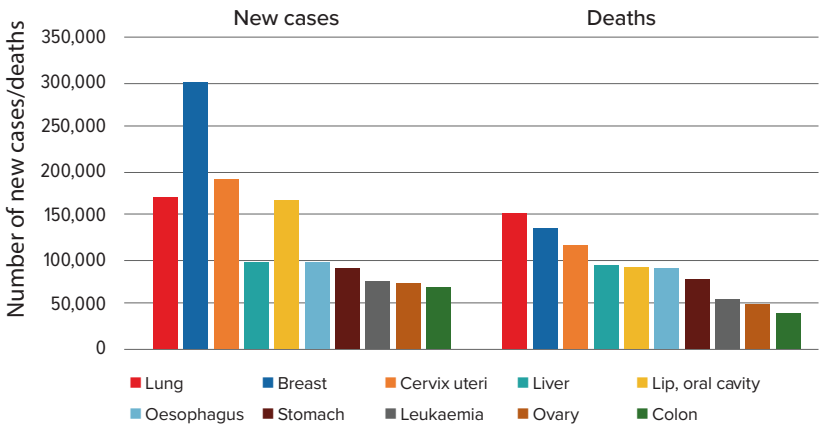
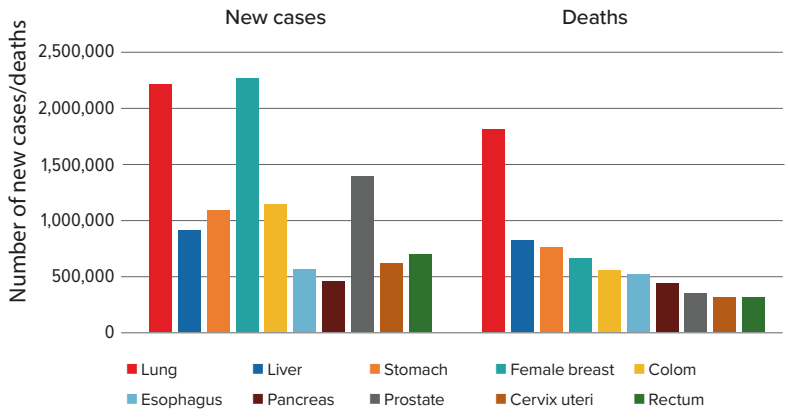
For decades, the public health community has sought to detect cancer more rapidly and effectively in asymptomatic people, and for good reason. By identifying cancer at an early stage or before symptoms appear, clinicians are able to dramatically decrease cancer-associated mortality. By the same token, cancer screening plays an increasingly important role in insurance medicine. While false-negative and false-positive test results do occur, these increasingly sophisticated tests play a vital role in the diagnosis and treatment of this disease globally, and insurers would do well to take stock of the current state of cancer screening. In Asia, in particular, national cancer screening programs offer a case study in how early detection of breast, cervical, and colorectal cancer can improve outcomes.

When looking at cancer incidence and mortality across the Asia region, high incidence is seen for lung, colorectal, and liver cancer for males, and in breast and cervical cancer for females. In addition, higher mortality is seen in lung and liver cancer for males, and in lung, breast, and cervical cancer for females. National cancer screening therefore corresponds to those cancers of high prevalence and high mortality.

Cancer Incidence and Death in South Eastern Asia[1]



Cancer Incidence and Death Globally[2]



While screening is almost universal for the most common and fatal cancers, ages at which screening is recommended can differ by organ. For example, breast cancer screening begins at age 40 in Korea and Japan, or at younger ages when compared with other screening tests. This is driven by data in many cases. For example, in Japan, a bimodal pattern in breast cancer incidence occurs, in which incidence peaks at around age 40 and again at age 60, so the screening recommendation reflects this pattern. In contrast, in the U.K.[3], individuals who began breast cancer tests before age 40 were found to show improved outcomes, suggesting the need for earlier screening in this population.

Lung cancer screening follows a similar pattern, varying by population and incidence. Lung cancer screening is recommended only in Japan. All employees need to have a chest X-ray once every five years starting at age 20, and then every year from age 40, based upon that nation's Industrial Safety and Health Act. In contrast, the most recent U.S. 2021 screening guidelines recommend low dose CT only for those with a history of smoking[4]).

Similarly, screening of gastric cancer is recommended in Korea and Japan, reflecting the high incidence in these countries. But in the case of liver cancer, which is less common, screening occurs only among high-risk groups.

The following table shows the age at which screening is recommended in a representative grouping of countries from across the developed world.

Table: Recommendation of screening

	Breast	Cervix	Colon	Stomach	Liver	Lung
KOR[5)]	40≦	20≦	50≦	40≦	40≦, high risk	
HK[6)]	******	25-64	50-75		/////	/////
SG[7)]	50-69	25≦	50≦		High risk	/////
JPN[8)]	40≦	20≦	40≦	50≦		40≦
AUS[9)]	50-74	25-74	50-74			
NZ[10)]	45-69	25-69	60-74			
UK[11)]	50-71	25-64	60≦			
US[12)]	50-74	21-65	50-75			50-80, smoker

///// Not recommended

****** Insufficient evidence to recommend

It is important to note that screening performed as part of a self-referred health checkup tends to cover more organs than population screening and could result in more insight into overall risk. People who can afford to pay for private checkups tend to be willing to pay for high-risk disease screening. These may include PSA screening for prostate cancer or thyroid cancer screening using thyroid ultrasound, or other tumor markers that are not recommended for mass population screening owing to the risk of overdiagnosis and overtreatment.

Looking ahead, more advanced screening technology using liquid biopsy or multi-gene panel testing may also be offered in the future. There is a potential risk of anti-selection whenever wider access to screening tests becomes available, just as misinterpretation and self-diagnosis can result from some direct-to-consumer tests. It is essential that a healthcare provider is available to explain screening results and empower individuals to make informed choices, just as it is critical that shared decisionmaking can take place between insurer and insured.

Notably, cancer screening seems likely to continue to contribute to early detection of cancer in Asia and around the world. Already, screening has resulted in a stage shift, or an increase in incidence of carcinoma-in-situ (CIS) lesions. In many cases, more expansive and comprehensive screening programs have led to a widespread leap forward in medicine, detecting lesions at early stages more frequently. For example, Bleyer A, et al. 13 reported on the effects of three decades of mammography screening for breast cancer in the U.S. since 1976. The study found that detected cases of early-stage breast cancer doubled with mammography screenings; on the other end of the spectrum, late-stage cancer incidence decreased by 8%.

This has obvious mortality and morbidity benefits, but can also support improved risk assessment in ways that are less well recognized. For example, a remarkable increase in incidence of thyroid cancer in Korea has been reported since that nation launched a national thyroid ultrasound screening program. This impacted critical illness portfolios that are priced based on disease incidence. In some markets, such as China, an increase in incidence of early lung cancer has emerged that can be linked to a national lung cancer screening program. More information, put simply, can lead to greater insight and improved medical underwriting assessments.

COVID-19 has placed some of these gains in temporary jeopardy. Lockdowns and social distancing mandates impacted standard of care screening and limited access to cancer screening in many nations. For example, some studies suggest gains in early detection of breast and colon cancers may be reversing due to screening delays.[14, 15] The long tail impact of COVID-19-related screening challenges on cancer incidence is still largely unknown.

In summary, insurers must be mindful that screening impacts both cancer survival and incidence. While there has been some advancement in imaging technology, current screening methods are generally inefficient and have resulted in both overdiagnosis and overtreatment. That said, preventive healthcare is important, and screening in its current form is foundational to detecting and, thus treating, disease. It is important to ensure that screening take-up rates are optimized at the appropriate ages together with the necessary pre-screening counseling. Risks and benefits of current screening modalities need to be weighed.

Insurers should recognize that the landscape of early cancer detection is evolving. The industry will need to learn from the past and factor this into trend assumptions in the future, to accommodate any medical advances that may change the current status quo.

The Future of Cancer Screening:
Targeted and Comprehensive

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There is significantly more that is understood today regarding the molecular basis of cancer. As a result, innovation and advances in both genomics and technology increasingly enhance clinicians' ability to detect cancer early. This could be through identifying lesions that may not progress to cancer, thereby reducing overdiagnosis; detecting underdiagnosed established lesions; or identifying those with a high probability of progression to cancer.

The future of cancer screening will likely rest on the identification of at-risk individuals (ultimately to include the general population) through risk stratification profiles incorporating genomic and environmental factors. It is estimated that by increasing diagnosis of early-stage cancers by 20%, mortality could be reduced by 15% within five years.[1]

Still, it is important to note that although many modalities for early cancer detection exist, adverse outcomes are not uncommonly encountered. These include false positives leading to unnecessary biopsies and other costly investigations, as well as the detection of indolent lesions (overdiagnosis), and subsequent overtreatment.

Furthermore, there are several cancers for which widespread screening is currently unavailable. Consider that currently available screening for breast, lung, colon, prostate, lung, and cervical cancers combined potentially detect fewer than half the number of diagnosed cancer cases overall. Given that each organ is screened individually, this is relatively inefficient. Complicating matters, screening program adherence rates are sub-optimal, even in communities where population screening options are affordable and widely available.

New developments in cancer detection may change this calculus. Here are some medical advances that are transforming the screening landscape and may have profound insurance implications.

Accessible Home Screening

Current screening efforts are not without logistical challenges. As with many other routine health visits, population screening drives were significantly impacted by the shelter-in-place orders implemented because of the COVID-19 pandemic. In the U.S., for example, an early analysis revealed a drop in screening of 94% for both breast cancer and cervical cytology screening, and 86% for colorectal cancer (CRC) screening. A recent commentary suggested the relatively lower drop in CRC screening was owing to alternatives to colonoscopy screening using home-based alternatives like the guaiac fecal occult blood test (gFOBT), fecal immunochemical test (FIT), and multitarget stool DNA (mt-sDNA) Cologuard test. These are indeed advantageous over colonoscopy screening since they can be carried out at home. Home sampling kits are also available for human papillomavirus testing for cervical cancer as an alternative to the in-office standard of care Papanicolaou (Pap) smear test. The authors highlight these approaches for

home cancer screening, in addition to telemedicine, as plausible future options for cancer screening. These may be useful for cancer prevention in more remote areas, or during a pandemic or similar crisis where access to healthcare is restricted. Overall, however, home screening would be limited by the number of cancers that can be screened for in this way.[2]

Targeted Risk-Profiling

Precision medicine, an emerging and more targeted gene-environment-lifestyle approach to disease management, is also being considered for preventive interventions, including screening.[3,4] Risk assessment is central to precision screening. Rapid scientific and technological advances should allow for a more accurate stratification of at-risk individuals who may benefit from prevention strategies, either increasing or decreasing surveillance according to the magnitude of each risk profile.

In the future, we may see more risk-stratification in screening using algorithms like the National Cancer Institute's Population-based Research to Optimize the Screening Process (PROSPR). This approach potentially reduces harm by allowing a more targeted preventive care approach. Furthermore, tools such as PROSPR could enable more effective communication and a deeper understanding of public perception of risk information, including its psychological consequences and linkages between risk data and the adoption of healthier lifestyle behaviors.

The behavioral science aspect of screening is likely to be enhanced over time. Undergoing a screening test makes cancer more salient and, as such, could present an opportunity for additional cancer prevention and early detection advice and education. As more screening tests become available, including more easily accessible direct-to-consumer products, empowering people to make more informed decisions about screening will become even more crucial.[5] The clinical costs and benefits, strengths, and weaknesses of this approach still need to be fully explored.

Insurance impacts of more individualized, risk-stratified screenings would depend upon levels of information symmetry between the general public and the industry. A better understanding of risk by the consumer could certainly be leveraged as part of a comprehensive wellness solution.

Polygenic risk scoring (PRS) could be used in clinical settings to help identify those with higher cancer risks, potentially leading to more personalized screening programs. In a study by Mavadatt and colleagues6 looking at breast cancer and its genetic risk, women whose PRS were in the top 20% were shown to have a higher lifetime incidence of breast cancer compared with women in the lowest quintile (17.2% vs. 5.3%). Earlier screening intervention could be recommended in those women with higher genetic predisposition, as these high-risk women could develop breast cancer well before the usual age for population screening.

The Women Informed to Screen Depending on Measures of Risk (WISDOM) study is currently underway and designed to compare annual versus risk-based screening (based on clinical risk factors such as BMI, age, breast density, and polygenic risk score) for breast cancer. The efficacy of this approach will be determined through the number of biopsies performed and the measurement of morbidity outcomes.[7]

Targeted Multi-Cancer Screening

The true future of cancer screening lies in pan-cancer early detection technology. Enter the liquid biopsy.

Cancer is, arguably, a genetic disease. In a simplified model of tumorigenesis (cancer development), genetic mutations due to environmental exposures or DNA copying errors accumulate, impacting the functionality of the cell and eventually leading to cancer. Research would suggest five to ten genetic alterations are required to induce a malignant phenotype (manifestation). The somatic mutations making up the biological signatures unique to a given tumor can be profiled, making these findings not only tumor-specific, but also more distinctive to a cancer compared to normal tissue. Yet, despite significant advances in effective cancer treatments including immune- and gene-directed therapies that target some of these known cancer mutations, cancer-specific mortality has only marginally improved for most solid tumors.

Leveraging the same technological advances and insights into cancer pathophysiology to find cancers at an early stage would offer the largest probable benefit – with cure rates five to ten times higher compared to cancers diagnosed at a late stage. Universal multi-cancer early detection (MCED) based on a combination of circulating biomarkers has the potential to transform

early cancer detection, particularly for those cancers with no currently available screening modalities (the current design of these non-invasive MCED tests requires application in conjunction with standard cancer screening testing).[8]

Key features of an early detection test would be:

- Good sensitivity and specificity for a clinically detectable cancer, the latter being most relevant in a population without high known or suspected cancer prevalence.
- Indication of the possible tissue of origin to direct any required targeted workup, thus avoiding diagnostic odysseys and associated mental and physical morbidity.

Current recommended single-cancer screening tests have false positive rates of around 9% to 14.5%, much higher than what is seen with MCED testing.

Liquid biopsies have been at the forefront of this advancement. This minimally invasive technique is performed on blood or other body fluids for measuring microscopic levels of cancer signals (i.e., diagnostically significant tumor-derived biomarkers). These include circulating tumor cells; circulating extracellular nucleic acids (cell-free DNA (cfDNA), and its neoplastic fraction or circulating tumor DNA (ctDNA) that shed likely from necrosis or apoptosis); as well as extracellular vesicles (such as exosomes), metabolites, and a variety of glycoproteins. From available data, approximately 0.1% to 89% of cfDNA is made of ctDNA, and the ratio increases as a cancer progresses. These biomarkers can be analysed using polymerase chain reaction (PCR) and/or next generation sequencing (NGS) for a number of derangements, including point mutations, copy number variations (i.e., alterations and amplifications), as well as microsatellite instability and high tumor mutational burden (parameters used for predicting immune treatment response).

The detection of tumor-derived RNA and DNA methylation patterns in the plasma reflects another non-invasive early cancer detection methodology, which provides complimentary information to the somatic mutations detected in ctDNA.

The many different uses of liquid biopsies in the management of cancer are beyond the scope of this article and have been addressed in the RGA Knowledge Center in more detail. However, its use in early cancer detection is significant; we will expand upon two emerging techniques – ctDNA and cfDNA, neither of which are currently available outside of clinical trials.

ctDNA

ctDNA is essentially a more direct biomarker for cancer detection and, as such, arguably more tumor-specific compared to known tumor markers and other surrogates, such as proteins and metabolites.[9, 10] This makes ctDNA an attractive tool to aid early cancer detection. Being able to serially measure ctDNA to functionally stratify more clinically indolent versus more consequential disease would help avoid overdiagnosis and overtreatment. ctDNA has a relatively short half-life of 30 minutes to two hours.

However, there are limitations in using ctDNA for early cancer detection:

- **Biological challenges** – Tumor heterogeneity by way of both inter-and intra-tumor genetic diversity is significant, and the individual tumor microenvironment and immune system interactions also impact each tumor's evolution and behavior.
- **Technical challenges** – Although easily obtainable from a blood draw, ctDNA also requires increased sequencing breadth and depth compared to tumor genotyping and monitoring. In fact, ctDNA needs to cover at least 10 times more genes (breadth) and requires 100 times the amount of sequencing (depth) to arrive at a result. Furthermore, the size of the studies for clinical validation and utilization would need to be an order of magnitude higher to confirm the technology's applicability to a particular cancer, especially as the target population for screening is asymptomatic individuals. Large and healthy control groups and longer clinical follow-up durations are required, given that non-cancerous normal tissue may have somatic mutations indistinguishable from cancerous tissue. An even lower limit of detection would be required given the low level of signal (smaller amounts of ctDNA) in early stage disease. All these technical challenges would have significant cost implications. The implementation and scalability of the technology

is a further consideration. Despite ongoing global efforts to catalog disease states and potential genetic targets, widely testing ctDNA screening appears to be outside of population-level feasibility.[4]

- Accumulating somatic mutations in solid and the haemopoietic systems (clonal haematopoiesis of indeterminate potential or CHIP) that increase with age also potentially confound ctDNA's utility. As a result, targeted sequencing with single nucleotide-variant-based classification would require concurrent sequencing of white blood cells (WBCs) to return accurate results.

CancerSEEK is a blood-based liquid biopsy test that detects eight common cancers (ovary, liver, stomach, pancreas, oesophagus, colon/rectum, lung, and breast) using a panel of 61 mutations in ctDNA, as well as 41 serum protein biomarkers. In a study involving 1,005 patients and 850 healthy controls, the detection of cancer had a specificity of 99% and sensitivity of between 69% and 98%, with sensitivity appearing highest for ovarian cancer (98%) and lowest for breast cancer (33%).11 The sensitivity and specificity of this study may have been skewed: there were more advanced cancers in the study group as compared with the general population, and this produces a higher sensitivity. The absence of chronic inflammatory conditions in the control group may lower the test's specificity. The test was also able to determine the type of cancer in a median 63% of individuals.

A more recent 2020 exploratory study using CancerSEEK-DETECT-A (Detecting cancers Earlier Through Elective mutation-based blood Collection and Testing) - was carried out on 10,000 women aged 65 to 75 with no prior history of cancer, confirming the feasibility and safety of the test.12 Positive blood tests were independently confirmed by a diagnostic PET-CT. In total, 96 cancers were diagnosed during the 12-month study. Twenty-six cancers were detected in ten organs, including nine lung and six ovarian cancers. Sixty-five percent of cancers were localized or regional. Twenty-four additional cancers were detected by standard-of-care screening and 46 by neither approach. One percent of participants underwent PET-CT imaging based on false-positive blood tests, and 0.22% underwent an unnecessary invasive diagnostic procedure. The authors noted that there was no change in usual screening behaviors in the study participants, suggesting that such testing can be incorporated into routine clinical care without discouraging participants from engaging in standard-of-care screening. CancerSEEK is not yet incorporated into clinical practice and is pending further validation.

Tumor-Derived RNA and DNA Methylation Patterns – DNA Methylation Signatures

Another recently used methodology involves the assessment of cfDNA methylation patterns. Methylation is an epigenetic change in which a methyl group is attached to the DNA, switching certain genes on or off as a result. Methylation is measurable. Increased methylation of tumor suppressor genes has been shown to be an early initiating event in tumorigenesis in carcinomas.

A prospective case-control observational study,[13] part of the Circulating Cell-free Genome Atlas (CCGA) study, evaluated the performance of pan-cancer targeted methylation analysis of >100,000 informative methylation regions of cfDNA with 6,689 participants (2,482 were diagnosed with over 50 types of cancer and 4,207 were healthy controls) using a single-draw blood test. Specificity was 99.3%. Overall sensitivity was 43.9% for all cancer types (stages I to III), with test performance varying by stage (39% in stage I, 69% in stage II, 83% in stage III, and 92% in stage IV). Sensitivity for 12 pre-defined cancer types that cause one-third of U.S. cancer deaths (anus, bladder, colon and rectum, oesophagus, head and neck, liver and bile duct, lung, lymphoma, ovaries, pancreas, and stomach, and plasma cell neoplasms) was 67%. The test had a 93% accuracy for detecting cancer-like signals (i.e., for tissue of origin localization).

A further and final clinical validation sub-study of the CCGA study[14] supported the feasibility of the same blood-based MCED test in an independent validation cohort as a complement to existing single-cancer screening tests with a similar specificity and sensitivity across different stages, and a slightly lower overall accuracy of tissue-of-origin localization in true positives of 88.7%. The importance of this accuracy metric is to help clinicians more clearly direct diagnostic workups after a positive test result.

The positive predictive value (PPV) (i.e., the likelihood that an individual with a positive test truly has the disease in the 50 to 79 years age group) was 44%. PPV is driven by specificity and population incidence. Specificity was consistent across age groups. This group will be followed up for five years. The intention is to complement existing screening as the sensitivity of screen-detected cancers such as breast and prostate cancer was lower overall.

A randomized control trial of this MCED test, called Galleri, will take place in 50- to 77-year-olds in the United Kingdom through its National Health Service (NHS). The trial aims to recruit 140,000 participants initially and 1 million by 2025. Controls will continue to have routine screening. All positive tests will be referred for additional diagnostic workup after a maximum two-week wait. If successful in reducing cancer mortality, this could possibly become part of routine screening in the U.K. by 2030.

A more widely used test in China is ELSA-seq, trialled in the THUNDER-II (THe UNintrusive Detection of Early-stage canceR) pilot study, which demonstrated that early cancer signals could be identified with high specificity.[15] The test detects signals from the liver, colon/rectum, oesophagus, pancreas, lung, and ovaries. The validation set results demonstrated 98.3% specificity and 80.6% sensitivity across disease stages and the different cancer types. Tissue of origin results were localized in 98.6% of cases, and 81% of these predictions were correct. A further prospective, multicenter, longitudinal PREDICT study aiming to identify multiple cancers non-invasively at early stages is underway.

Insurance Implications

The ability to detect cancer at early stages has the potential to reduce cancer mortality. Some estimates suggest cancer detection before stage IV could reduce cancer-related deaths.[1] The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program estimates a 16% reduction in deaths if stage IV cancers were diagnosed at stage III, and a 24% reduction if diagnosed at stages I, II or III instead (assuming an equal one-third distribution for a diagnosis at each lesser stage). This reduction in all-cause mortality would be comparable in magnitude to eliminating deaths due to cerebrovascular disease, according to the authors. Each cancer death in the U.S. reportedly results in an average of 15.6 years of life lost.

From a morbidity perspective, the potential impact is an increase in cancer incidence rates with an overall incidence higher at younger ages, and a shift to diagnosis at an earlier stage. This could offset a late-stage impact in a staged product; however, if pan-cancer screening tests become a viable option for population screening a greater concern would be the potential for overdiagnosis and an increase in cancer incidence rates. This could have a significant impact on in-force products with guaranteed pricing as well as for any new product pricing.

Increased anti-selection at underwriting could result from more applicants with positive screening tests selectively purchasing products that pay on the diagnosis of cancer.

Conclusion

Mindful of how new advances in screening might impact risk assessment, incidence rates, and outcomes of cancer, the development of more targeted approaches including MCED testing will likely transform cancer screening in the future. Close attention needs to be paid to these significant advancements. As with many new medical breakthroughs, the benefits and risks will need to be weighed, and accommodated in any risk assessment approach and modeling assumptions.

Either way, growing awareness of the need for cancer screening and a shift toward preventive healthcare, higher access to screening tests, better compliance, increased risk-communication, and additional risk-stratification – combined with the use of potentially revolutionary technology – may transform the cancer treatment landscape in the not-too-distant horizon. This is a trend for which the insurance industry will need to make provisions and watch closely.

Cardiac Screening Toolbox: Exploring Available Tools and Techniques

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In recent years, the incidence of cardiovascular diseases has increased; at the time, diagnosis and treatment costs continue to rise. As a result, clinicians, patients, and insurers alike have increasingly come to rely on screening for cardiovascular disease. And yet, underwriters may not have a full understanding of how screening can be applied in clinical investigations to identify common cardiovascular disease risks, especially in applicants at high or intermediate cardiac risk.

Keep in mind that screening is different from diagnosis. The primary purpose of screening is to detect early disease indicators, or risk factors for disease, in large numbers of apparently healthy individuals. In contrast, the purpose of a diagnostic test is to establish the presence (or absence) of disease as a basis for treatment decisions in symptomatic individuals or to confirm a disease finding in patients who have already tested positive. In short, screening empowers clinicians to discover risks, while diagnostic tests help patients and their healthcare providers confirm a course of treatment.

Notably, insurers can use medical screening to discover common risks within the general population, and nowhere is this more apparent than in detection of cardiovascular diseases. Insurers can select cardiovascular tests that are cost-effective, convenient, non-invasive, relevant (targeting common risks), and accurate (as close as possible to the gold standard of clinical diagnosis). It is important that underwriters understand the following benefits and limits of each form of cardiac screening before making a request and must keep in mind that the pretest possibility of one disease can influence the value of the screening investigation.

Electrocardiogram (ECG)

The most basic screening for cardiac disorders, the ECG, can also offer insight into risks in those who have non-cardiac disorders.

ECGs can detect heart rate and rhythm changes, erratic voltage and axis readings, abnormal wave/segment/interval changes, and similar signals that could indicate a need for further investigation of ischemia, arrhythmia, and structural heart diseases, and other cardiac disorders.

What is less appreciated is that the ECG screening can also help insurers identify non-cardiac disorders, such as COPD, thyroid dysfunction, and obvious anemia. ECG represents the first line of risk screening and can induce a need for further investigation. Asymptomatic persons with resting ECG abnormalities such as ST depression, T-wave inversion, left ventricular hypertrophy or strain, and premature ventricular contractions have a two- to ten-fold increased risk of cardiovascular disease (CAD) when compared with those with normal ECG results. In different epidemiologic studies, the presence of variably defined ECG abnormalities has increased the adjusted relative risk for cardiovascular mortality and morbidity by 1.5- to 2.5-fold.

ECGs are not foolproof, however. Many individuals with angiographically proven CAD have normal resting ECG results, and most coronary events occur in individuals without resting ECG abnormalities. Fortunately, we have other screenings with better sensitivity.

Exercise Stress Testing

Exercise stress testing has been used for decades as a noninvasive test to diagnose and risk stratify CAD. The overall sensitivity has ranges from 60% to 70%, with a specificity of 85%. Patients at moderate risk for CAD are best served with this screening test, except for females during their reproductive years when a high incidence of false positive results has been reported.

In many ways, exercise stress testing can complement ECG-change interpretation because of its strong prognostic value. For example, screening exercise ECG testing was performed in more than 10,000 subjects who participated in the Multiple Risk Factor Intervention Trial (MRFIT) and the Lipid Research Clinic's Coronary Primary Prevention Trial (LRCPPT). In the study, baseline treadmill exercise testing detected asymptomatic ischemia and accurately predicted an increased risk of coronary events and cardiac death within seven to ten years.

Similarly, studies have established that the higher the pretest probability of CAD, the higher the value of the exercise stress test. Exercise capacity is an important indicator of cardiovascular mortality, and information collected during recovery stages of the exercise test is very valuable in identifying risk. For example, in a study of 2,994 asymptomatic women who underwent exercise ECG testing and were followed for 20 years, exercise-induced ST segment depression (≥1.0 mm) did not increase the risk of cardiovascular death (age-adjusted hazard ratio [HR] 1.02). By contrast, women who were below the median for both exercise capacity and heart rate recovery, which were considered measures of fitness, had a 3.5-fold increased risk of cardiovascular death (95% CI, 1.57-7.86) compared with those above the median for both variables.

The enlightenments of these observations to insurers include: the higher the pretest probability of CAD, the higher the value of the exercise stress test; exercise capacity is a critical indicator of cardiovascular mortality; and information collected during recovery stages of the exercise test is valuable in identifying risk.

Holter

The Holter employs the use of portable ECG that records continuously for 24 hours or longer. Its primary purpose is to identify arrhythmias and assist clinicians in investigating those with a syncope and presyncope. Due to the poor sensitivity and specificity, Holter is not recommended as a screening tool for coronary artery disease. However, it is a first-line test for arrhythmia and conduction abnormalities.

The Holter is the most widely employed technology for the evaluation of a patient with symptoms suggestive of arrhythmias. Insurers may also consider using this screening tool with asymptomatic applicants with incidentally found arrhythmia on a resting or exercising ECG test.

Once a Holter is complete, underwriters may base a decision on the resulting type, frequency, or severity of any arrhythmia that may be detected, or the underwriter may instead wish to pursue further cardiac investigation.

In the Holter report, there is another important indicator – HRV (heart rate variability) – which is usually reported using SDNN (standard deviation of NN intervals). Low HRV has been regarded to be independently predictive of increased mortality in patients' post-myocardial infarction or with heart failure. It is also regarded as predictor of SCD (sudden cardiac death).

While the Holter screening can detect arrhythmia and conduction abnormalities, it cannot reveal the exact origin of the abnormality, yet origin-related information is closely related to the severity of the condition and to further treatment plan. An electrophysiologic study (EPS) can offer a clearer picture of arrhythmia; this study offers a detailed analysis of the mechanism(s) underlying the arrhythmia, locates the site of origin precisely, and can lead to treatment via catheter-based ablation technique, when necessary.

CAC score and CTCA (CT Coronary Angiography)

During medical underwriting, once ECG (resting or exercise) has determined that a ST-T change is suspected due to ischemia, further screening can be performed with CT to obtain a coronary artery calcium (CAC) score or to perform noninvasive CTCA. The association between the presence and severity of CAC and the risk of cardiovascular events has been demonstrated since the late 1950s.

Coronary artery calcium data and reporting system (CAC-DRS) is a new standardized reporting system for calcium scoring on computed tomography. Four CAC-DRS categories have been described ranging from CAC-DRS 0 to CAC-DRS 3, with progressively increasing cardiac disease risk (very low, mild, moderate, and moderate to severe).

The higher score is associated with progressive atherosclerosis and increased coronary artery stenosis, but CAC-DRS 0 & 1 (very low and mild risk) cannot exclude obstruction stenosis. Clinically, CAC screening is not recommended for low-risk and high-risk people.

Invasive coronary angiography is not recommended as a form of screening for CAD, although it is regarded as the 'gold standard' of diagnosis. Among available noninvasive tests, CTCA provides acceptable diagnostic accuracy for the exclusion of coronary artery disease. CTCA has the highest diagnostic accuracy for the detection of obstructive CAD defined as >50% luminal narrowing in major epicardial vessels as detected by invasive coronary angiography. When evaluated against clinical data, CTCA has high sensitivity and negative predictive value (NPV) of 95% and 94% respectively. From the insurer's view, any test with satisfactory sensitivity and NPV are ideal for screening purposes. The more sensitive a test, the less likely an individual with a negative test will have the disease, and thus the greater the negative predictive value. In other words, fewer cases of disease are missed.

CTCA is useful in patients with an uninterpretable ECG and in those who cannot exercise, especially the high-risk populations.

There are CAD-RADS categories to describe CTCA findings and to classify them according to management recommendations in patients with either acute or stable chest pain (such as BIRADS for breast imaging and TIRADS for thyroid imaging). CTCA can also find and evaluate the effect of myocardial bridging in coronary arteries, and other congenital or acquired coronary artery abnormalities.

Echocardiogram

Another common cardiac risk consideration is the discovery of a structural heart disorder. Echocardiography is a major noninvasive diagnostic tool that enables real-time imaging of cardiac structure and function and regarded as first-line screening for structural heart diseases. It can detect a congenital heart defect even before birth. Enhancing agents can be given intravenously and sometimes transesophageal echocardiogram is needed for clearer imaging. Doppler technique is now generally used to check blood flow and blood pressures. The echocardiogram is recommended when any heart murmur is noted, when cardiomegaly is suspected based on chest X-rays, or when ECG findings reveal abnormalities of chamber size, wall thickness, or pericardial- or valvular-related issues.

Besides empowering clinicians to screen for structural heart disease, the echocardiogram provides powerful parameters for risk stratification after acute myocardial infarction (AMI). In particular, the echocardiogram provides a left ventricular ejection fraction, wall motion score index, and diastolic measurements including E velocity deceleration time and E/e' ratio. All of these metrics equip the underwriter to better assess risk and provide information on short- and long-term outcomes after AMI.

Remember, however, that the echocardiogram remains largely reliant on the subjective interpretation of the analyst and his or her level of expertise. Misinterpretation and wide variation are long-standing issues, especially when images are of poor quality.

With advancements in digital technology and digital image processing, ultrasound systems became smaller and lighter to where they can be hand-held and carried in a coat pocket. Current hand-held systems

provide two-dimensional images and color-flow doppler of diagnostic quality. This allows physicians to examine patients at the bedside so they can rapidly assess ventricular and valvular function and screen for pericardial effusion and aortic root pathology. But results from this type of hand-held device are only as good as the operator. Whenever possible, underwriters would do well to assess whether a screening has been conducted by an experienced physician who has been provided the necessary training in the use of these sophisticated machines.

Exercise echocardiograms are another way insurers can assess risk, especially in cases in which it is difficult to distinguish whether a ST-T change is due to a conduction issue or ischemia (e.g., bundle branch block (BBB) - Right BBB, Left BBB, or pre-exciting syndrome). Here, clinical data demonstrates that the exercise echocardiogram has better sensitivity than an exercise ECG in detecting cardiovascular disease.

Cardiac Magnetic Resonance Imaging / Cardiovascular Magnetic Resonance

Cardiac magnetic resonance imaging (MRI), also referred to as cardiovascular magnetic resonance (CMR), is the preferred method for assessment of functional and tissue properties of the heart, including atrial and ventricular anatomy and motion, and myocardial tissue composition.

CMR enables further evaluation of the myocardium for ischemia (e.g., perfusion, viability, and scarring), inflammation, or infiltration. In addition, CMR is used to further evaluate suspected valvular dysfunction, pericardial disease, suspected cardiac tumors, and coronary artery anatomy. CMR can help exclude arrhythmogenic right ventricular cardiomyopathy (ARVC), amyloidosis, and sarcoidosis, among other diseases. CMR can also evaluate the presence and extent of myocardial fibrosis in patients with left ventricular dysfunction. In short, CMR is used to diagnose more complex structural or functional cardiac diseases, informing treatment plans. Underwriters should note that given its high cost and complex operation and interpretation, CMR is not used as a first-line screening method.

Other Tests

Some blood tests are also used to screen risks for cardiovascular diseases, but they are not regarded as clinical screenings. Due to specific market norms and legal limitations, genetic tests are not used to screen insured populations for cardiac disorders. Occasionally, underwriters may encounter a myocardial perfusion scan report during the medical underwriting stage. This is a nuclear medicine procedure that illustrates the function of the myocardium during rest or under stress, which can help to rule out ischemic heart disease, or to assess myocardial damage after a heart attack. Due to radiation exposure and the complexity of the procedure, this type of nuclear scan has been largely replaced by CTCA or stress echocardiogram.

Conclusion

When it comes to a wide range of cardiac disorders, it should be reiterated that screening is different than diagnostic examinations. Whenever possible, insurers should follow best practices and request cost-effective, non- or minimally invasive, simple and convenient clinical methods to assess risk. Remember, underwriters are screening the risks, underwriting them accordingly if we can. Diagnosis lies with the healthcare professionals who can treat these patients.

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