Opinion Paper

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The side effects of translational omics: overtesting, overdiagnosis, overtreatment

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Abstract: High-throughput technologies such as next-generation genomics, transcriptomics and proteomics are capable of generating massive amounts of data quickly, and at relatively low costs. It is tempting to use this data for various medical applications including preclinical disease detection and for prediction of disease predisposition. Pilot projects, initiated by various research groups and Google, are currently underway, but results with not be available for a few years. We here summarize some possible difficulties with these approaches, by using examples from already tried cancer and other screening programs. Population screening, especially with multiparametric algorithms, will identify at least some false positive parameters and screening programs will identify abnormal results in otherwise healthy individuals. Whole genome sequencing will identify genetic changes of unknown significance and may not predict accurately future disease predisposition if the disease is also influenced by environmental factors. In screening programs, if the disease is rare, the positive predictive value of the test will be low, even if the test has excellent sensitivity and specificity. False positive results may require invasive procedures to delineate. Furthermore, screening programs are not effective if the cancer grows quickly, and will identify indolent forms of the disease with slow-growing tumors. It has also been recently shown that for some cancers, more intensive and radical treatments do not usually lead to better clinical outcomes. We conclude that new omics testing technologies should avoid overdiagnosis and overtreatment and need to be evaluated for overall clinical benefit before introduction to the clinic.

Keywords: escape from cure; high-throughput omics; incidental findings; indolent disease; overdiagnosis; overtesting; overtreatment; side effects.

Introduction

To paraphrase from the legal saying, "you are healthy until proven otherwise" or "you are sick until proven otherwise". These two versions of the saying have important ramifications. In the first version, you will seek medical attention only when you feel sick. In the second version, you will need to submit yourself to exhaustive examinations, to find out what illness you may have, and only when the full investigation finds nothing, you can declare yourself "healthy". If something does come-up during the investigation, you may try to fix the problem right away, even if it does not bother you or have any symptoms.

The range of available diagnostic tests is rapidly increasing, especially due to emerging Omics technologies and modern non-invasive sensors [1–3]. The most widely pursued clinical applications of these new technologies include testing of asymptomatic individuals to identify early disease symptoms or future disease predisposition. Proponents assume that extended testing, followed by aggressive therapeutic or preventative measures, should benefit those individuals [4]. Recently, highly recognized scientists [5] and leading technology-driven companies such as Google [6] have entered the diagnostic field with focus on early disease detection in asymptomatic individuals. These are primarily pilot studies which will likely last at least a few years and outcomes will not be known soon. However, the general strategies followed by the aforementioned and other studies are equivalent to population screening, which has been around for a while. In an era of evidence-based medicine and personalized

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treatments, we will examine here if already implemented population screening programs (i.e. testing asymptomatic individuals to identify pre-clinical disease) have already contributed to improved patient care, in an effort to predict the outcomes of the new studies. Some criticism of these studies has already been voiced elsewhere [7]. Apart from cost, we should keep in mind that successful programs should lead to benefits that outweigh harms.

The premise of population screening

Neonatal screening for phenylketonuria (PKU) and congenital hypothyroidism were successfully introduced more than 50 and 25 years ago, respectively. Advances in mass spectrometry expanded neonatal screening to approximately 50 rare disorders [8]. The most universally accepted criteria for screening, formulated by Wilson and Jungner [9], are as follows: the condition should be an important problem with a known natural history, and have an agreed policy on whom to treat. Diagnostic and treatment facilities should be available; there should be a suitable, acceptable test; and the cost of case-finding should be economically balanced in relation to medical costs as a whole.

It should be reminded that it is very costly to conduct prospective clinical trials to show effectiveness of screening for any disease. If the disease is relatively rare, as is usually the case with genetic diseases and some cancers, hundreds of thousands or millions of individuals need to be enrolled and monitored for a long period to show a possible benefit [8]. This is why prospective data on the effectiveness of well-established screening programs such as PKU are still lacking. The screening criteria mentioned above should be considered when new Omics assays are intended for testing asymptomatic individuals to identify preclinical disease.

One major and well-recognized concern with neonatal screening (and the situation is very similar with many adult diseases; see below) is that screening may uncover not only clinically significant cases which can benefit from early treatment, but also, sometimes larger numbers of cases who are asymptomatic [8]. Such positive results, but of uncertain significance, are confusing to the families and could lead to treatments that are not beneficial, adding anxiety to patients and families and costs to the medical system. These positive results are classified as "overdiagnosis". According to Welch [10], overdiagnosis is the detection of abnormalities that will never cause symptoms or death during a patient's lifetime.

Disease screening by biochemical profiling

The concept of biochemical profiling for asymptomatic disease diagnosis is not new. Continuous flow analysis (CFA), was discovered in 1957 and further perfected in the mid-1970s [11]. CFA facilitated the simultaneous and automated measurement of 50–100 analytes in biological fluids at no additional cost, as compared to one analyte. Thus, CFA was used to reveal biochemical changes of early disease signs in asymptomatic individuals. However, it was soon realized that such analysis will predictably lead to approximately 5% false-positive tests (i.e. test results outside the reference intervals in otherwise normal subjects). This is due to the definition of reference intervals as being values between the 2.5 and 97.5 percentile of a reference (normal) population. The high cost of investigating seemingly abnormal results in normal people, and the added anxiety of patients, has led to the complete replacement of biochemical profiling with what is now known as "discrete testing". In the latter, tests are performed by the testing laboratory, only if requested specifically by a physician. Any high-throughput multianalyte Omics testing strategy should take into account that a small percentage (i.e. 5%) of healthy individuals will have one or more abnormal parameters, and this could lead to additional unnecessary investigations and probably harmful interventions. These false positives could be reduced by extending the reference range, but in this case, the test's ability to identify disease (sensitivity) will also be reduced proportionally.

Whole genome sequencing (WGS)

There is now widespread discussion on the use of WGS for patient care. The issue of cost does not dominate discussions anymore, since the target cost of $1000 per genome has now been achieved [12]. Is this a good reason to do the test? As we described elsewhere [13], there are still many unresolved issues regarding WGS application in the clinic (technological, quality assurance, interpretative, ethical and, most importantly, efficacy-related). While WGS has been used for molecular characterization of genetic diseases of unknown etiology, current efficiency is rather low,

at 25% [14]. WGS for finding individualized treatments of cancer patients is a research front that is evolving, in parallel with new biological treatments [15]. Some reported data are highly promising but it is premature to draw any definitive conclusions [16]. Many authorities point to a number of challenges that need to be addressed before these approaches reach the clinic [17, 18]. WGS could be used to assess disease risk predisposition, so that preventative measures (if any) or therapeutic interventions can stop or slow down disease processes, such as neurodegeneration. Disease predisposition is currently assessed by identifying alleles (single nucleotide polymorphisms) associated with lower or higher risk for developing a disease in a lifetime. Direct-to-consumer testing for predicting disease predisposition is popular but the US Food and Drug Administration (FDA) has imposed restrictions for such testing, until the efficacy of the test is proven [19, 20]. Despite voices of luminaries, such as George Church, that WGS is clinically useful today [21], the analyses of Roberts et al. [22], derived from data of a large number of monozygotic twin pairs, have shown that WGS will likely not be effective in predicting disease predisposition since for most diseases, environmental factors are dominating over genetic factors.

In conclusion, the power of WGS for clinical use is well-recognized but many unresolved issues exist, especially when it comes to identifying genetic changes of unknown significance. These genetic changes may contribute to overdiagnosis and overtreatment.

Current experience with cancer screening

Cancer screening is based on the hypothesis that if cancer is detected early, when the lesion is small and localized, the chances of removing it completely, or treating it effectively, are higher; thus, screening should lead to better clinical outcomes. This is why the National Institutes of Health and associated organizations (such as the Early Detection Research Network) fund the development of new imaging technologies or biochemical markers that can detect early and localized cancer. One caveat with population screening is that even if the screening method is highly sensitive (i.e. is detecting most cancers) and highly specific (i.e. results are negative in most healthy individuals), if the disease under consideration is rather rare (e.g. 1 affected individual for every 1000 screened), a test with 99% sensitivity will detect nearly all (n=10) patients in 10,000 screened individuals; but at 99% specificity, there will be 10 times more false positives (FP) (n=100) than true positives (TP) (n=10), yielding a positive predictive value of only 10% [23]. This example underlines the inherent difficulty with population screening, which usually identifies a lot more FP than TP. Separating TP from FP is not trivial and it may necessitate invasive and potentially harmful procedures such as biopsies, laparotomies, or other major surgeries. An additional, already mentioned, major complication of screening is that it may uncover indolent forms of the disease; i.e. lesions that will not pose a threat to patient's life but grow slowly and likely remain undetected for long periods (overdiagnosis). But when detected, these lesions are usually treated (overtreatment), adding to the cost of health care and sometimes inflicting potentially serious side effects (Figure 1) [24].

There is another consideration regarding cancer screening. As discussed below, some screening programs are more successful than others. One contributing factor is disease heterogeneity and variable biological behavior. For example, for cancers that grow rapidly (such as invasive serous ovarian carcinoma) screening is not effective because many early stage cancers are missed in the first cycle of screening but found to already be metastatic in the subsequent round (after a year or two). But for the same cancer type, endometrioid and clear cell carcinomas, which grow less rapidly than serous histotypes, screening is more effective in identifying localized and potentially treatable disease. On the other hand, screening for slowly growing tumors (such as low grade prostate cancers) identifies cancers that are deemed indolent and not worth discovering since they will likely not pose a threat to patient's life.

The issues of sensitivity, specificity, positive and negative predictive value, disease prevalence, disease heterogeneity and biological behavior should be considered when new omics technologies are used for finding asymptomatic disease.

Successes and failures of cancer screening

A notable example of a successful cancer screening program is cervical cancer, for which there are unified recommendations for cytological screening every 3 years or combined cytological and HPV co-testing every 5 years [25]. Screening for colorectal cancer also decreases disease-specific death rate by approximately 30% [26]. However, colonoscopy-guided screening carries a

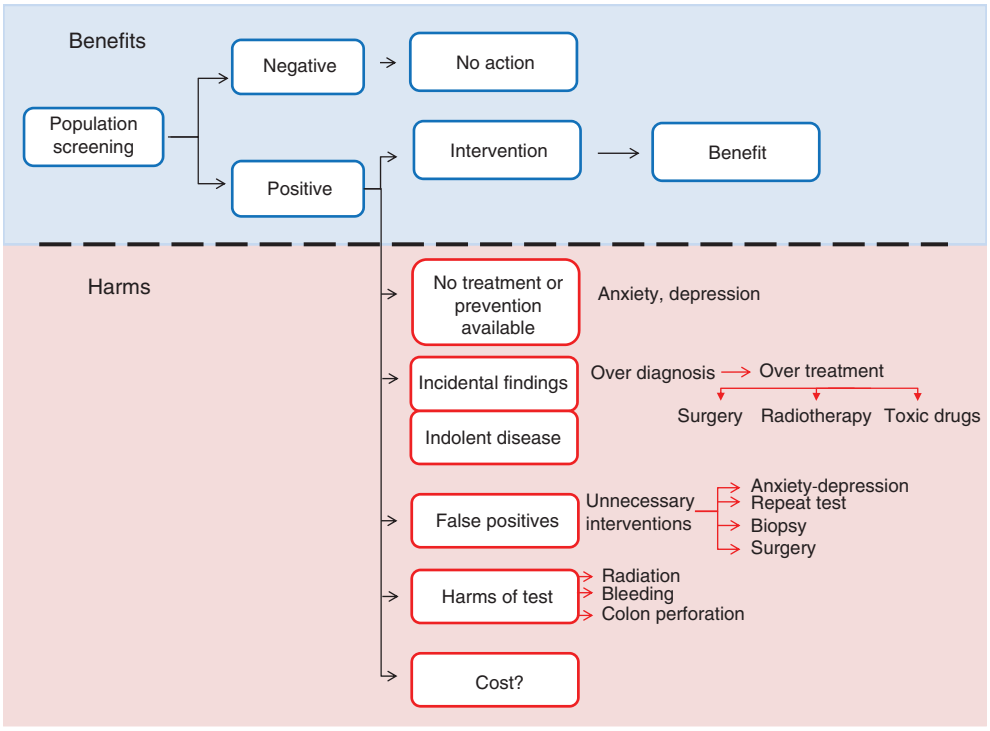

Figure 1: Benefits and harms of population screening strategies.
Indolent disease is defined as a disease that would have not been detected in the patient's lifetime without screening. Incidental findings are defined as entities that are unrelated to the primary reason of patient testing. These two terms are related. For more discussion see text.

complication rate of about 0.1%, including colon perforation and bleeding [27].

For breast cancer, for which there is a 30 years screening experience, it was recently estimated that the 30% decrease in the rate of death from breast cancer is due more to improved treatments, such as tamoxifen, rather than to screening [28]. Based on the cancers detected each year, it was found that screening increased the number of detected breast cancers from 112 to 234 cases per 100,000 women, an absolute increase of 122 cases per 100,000 women. However, late stage breast cancer detection decreased by only 8%; from 102 to 94 cases per 100,000 women. Based on these numbers, it was concluded that only eight out of 122 additional early-stage breast cancer diagnosed were expected to progress to advanced disease. This has led to the conclusion that overdiagnosis of breast cancer (i.e. tumors detected by screening that would have never led to clinical symptoms) was approximately 1.3 million in the past 30 years. It was also estimated that in 2008 alone, breast cancer was overdiagnosed (based on the above definition) in more than 70,000 women (31% of all breast cancers diagnosed). This data supports the view that screening for breast cancer can lead to substantial overdiagnosis and overtreatment, with only modest improvements in survival due to screening. Similar concerns about the effectiveness of breast cancer screening to reduce patient mortality have also been raised by others, and the suggestion was made that breast cancer screening should be abolished [29].

Lung cancer screening with low-dose thoracic computed tomography of heavy smokers reduces mortality from lung cancer by approximately 20% [30, 31]. However, lung cancer screening includes associated harms such as false-positive results, incidental findings and radiation exposure. False-positive results occur in a substantial proportion of the screened population; it is estimated that 95% of all positive results do not lead to diagnosis of lung cancer. The proportion of invasive diagnostic procedures in patients with one or more lung nodules is approximately 1%–4%. The risk of major complications is 4.5 per 10,000 persons screened and 25% of the surgical procedures in the nation's lung screening trial were performed on nodules that were later determined to be benign [32]. Overdiagnosis in lung cancer screening programs is defined as screen-detected cancer cases that would have not been detected in the patient's lifetime without screening. About 10%–12% of screen-detected cancer cases are attributed to overdiagnosis [33]. Thus, in lung cancer screening programs, the relatively small benefits need to be weighed against the costs, harms of exposure to radiation, the vast

number of individuals who have benign nodules and the invasive follow-up procedures in patients who do not have cancer or are overdiagnosed.

For ovarian cancer we do not as yet know the effect of screening on mortality [34]. However, preliminary data, by using either multimodal or ultrasound-based screening, reveal that the positive predictive value of such tests ranges from 35% (multimodal) to 2.8% (ultrasound). This means that for confirmation of diagnosis, more women without ovarian cancer will undergo invasive surgical procedures (such as laparotomy) than patients with ovarian cancer. The overdiagnosis in this cancer (as defined above) is still being investigated.

Despite the enthusiastic endorsement of screening for prostate cancer in the 1990s and 2000s, the prospective randomized clinical trials and meta-analyses have shown that the incidence of prostate cancer in the screening group has increased significantly [35, 36]. One of the studies [37] demonstrated that screening improves risk of prostate cancer-specific death but an additional 37 men needed to receive a diagnosis through screening, for every one saved prostate cancer death, after 11 years of follow-up. The harms associated with screening include false-positive results, overdiagnosis, overtreatment and complications of biopsy and treatment. Among men who are undergoing prostatic biopsy, 75% of them do not have cancer; side effects include pain, fever, hematuria, hematochezia and hematospermia. Side effects of radical prostatectomy include incontinence and erectile dysfunction. Other harms include anxiety and depression [38]. In order to maximize the benefits of PSA screening and reduce harms, it is now recommended that screening is restricted to men aged 55–69 years, in men who show definite preference for screening and that conservative therapy for men receiving a new diagnosis for prostate cancer is considered, especially in those patients who have low grade prostate cancer [39–41]. The PIVOT trial has shown that among men with localized prostate cancer, randomized to receive radical prostatectomy or active surveillance as a form of therapy, mortality was approximately the same after 10 years of follow-up [42, 43].

All these data have been cited to further emphasize the points that screening for cancer did not fulfill the premise of significantly improving patient outcomes, that screening may identify indolent forms of the disease, that screening could be harmful to many participants and that even the most high profile screening programs (breast, prostate, lung, ovarian) are still controversial. New omics technologies that are being used to identify asymptomatic disease are likely to be associated with very similar problems of safety and efficacy.

Iatrogenic morbidity

Iatrogenic morbidity is defined as preventable harm resulting from medical treatment or advice to patients. Iatrogenic morbidity is quite frequent and it is estimated that in USA, is causing approximately 200,000 deaths per year, and it is the third most frequent cause of mortality after cardiovascular events and cancer. Iatrogenic morbidity has been recognized by Hippocrates, and is included in his Oath ("first do no harm"). In the context of overtesting, overdiagnosis and overtreatment, iatrogenic morbidity includes complications of follow-up procedures such as biopsies and surgeries, prescription of toxic or ineffective drugs, and psychological effects such as anxiety and depression. Omics testing, in the future, should ensure that iatrogenic morbidity is minimized.

Incidentalomas

"Incidentalomas" have been described as a new entity, representing findings unrelated to the primary reason of patient testing [44]. Such incidental findings are highly prevalent with modern high-throughput technologies such as exome and whole genome sequencing, as well as imaging.

Follow-up investigation of incidentalomas may be highly complicated and includes unnecessary biopsies, surgeries and additional tests of patients and family members. One major problem of incidental findings with genomic testing is that the specific effects of many single variants of clinical relevance are currently unknown [45].

Withhold treatment until later: the concept of "escape from cure"

The new "omics" testing aims at disease diagnosis at the earliest possible time so that treatments are instituted, even in the absence of symptoms [5, 6]. Over the last 30 years, there have been important changes in our philosophy on when and how to treat serious diseases like cancer after diagnosis. Originally, it was thought that early radical treatments should lead to better results than later and less radical treatments, especially for localized disease. Fisher et al. demonstrated that lumpectomy and total mastectomy breast cancer treatments did not differ in outcome [46]. The PIVOT trial of prostate cancer intervention versus observation has shown that there are small differences in overall mortality between men who underwent radical prostatectomy (47% overall mortality)

and men who had been randomized for observation (50% mortality) [42]. However, subgroup analysis has shown that in patients with PSA ≤ 10 ng/mL at diagnosis (most of these patients are identified by screening), radical prostatectomy (overall mortality 46%) was not advantageous to observation alone (overall mortality 44%). In men with baseline PSA≥10 ng/mL the overall mortality was 48% with radical prostatectomy versus 62% with observation. This data suggests that men with PSA ≤ 10 ng/mL could be followed by observation alone, thus avoiding therapy and its side-effects, until PSA reaches the level of 10 ng/mL (the threshold of escape from cure) (Figure 2).

The less radical and delayed treatment strategies underline the point that it may not always be the case that early diagnosis and immediate administration of treatment leads to a better clinical outcome.

Closing remarks

First, it appears that some older and seemingly obvious dogmas, suggesting that serious progressive diseases (such as cancer) can be better treated with more radical surgical procedures and intensive adjuvant supplements, such as radiotherapy/chemotherapy, do not seem to always hold true. Also, the concept of "escape from cure" suggests that if such threshold is known, it may be worth postponing definitive treatments, since the outcomes appear to be similar, but quality of life is better. At least for prostate cancer, active surveillance (observation), is equivalent to highly invasive surgical procedures such as radical prostatectomy, especially for patients with early stage disease, discovered by using current screening protocols. So, the previously practiced philosophy of early intensive treatments could change to a more conservative approach, at least for some diseases.

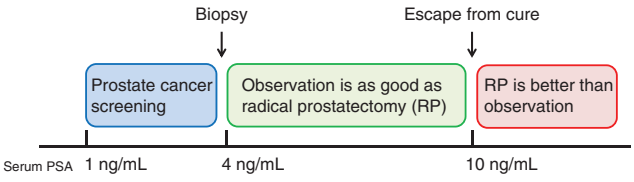

Figure 2: The concept of "escape from cure".
Data are based on the PIVOT trial [42]. For patients with localized prostate cancer, patients with a PSA≤10 ng/mL at diagnosis had similar overall mortality whether treated by radical prostatectomy (RP) (46%) or observation (44%). Beyond the "escape from cure" point (PSA>10 ng/mL), the overall mortality was superior with radical prostatectomy (48%) versus observation (62%).

Along similar lines, Esserman et al. lately suggested that when performing diagnostic procedures, the term "cancer" should be reserved to describe lesions with a reasonable likelihood of lethal progression, if untreated [24]. For premalignant lesions and indolent or low risk lesions, the term IDLE (indolent lesions of epithelial origin) should be preferable. This definition may spare many patients from the anxiety of being diagnosed with a malignancy.

The evolution of many omics technologies and modern imaging is giving us unprecedented opportunities to monitor hundreds, or even thousands of proteins in biological fluids as well as delineate whole microbiomes, genomes and exomes. The cost and turnaround times of such testing are rapidly declining. However, the examples provided suggest that more testing, especially of asymptomatic individuals, does not guarantee benefit and it could be harmful (Figure 1). Box 1 summarizes our experience with multiparametric testing, and population screening, with emphasis on anticipated difficulties in the context of new omics technologies.

There is no question the whole genome sequencing and other omics technologies will find their place in the diagnostic arena and used to benefit patients. However, until their usefulness is demonstrated with well-designed validation studies, they should be restricted for research purposes only. As mentioned by others elsewhere, "no request for an investigation should be placed, unless the physician is confident that the answer, and the actions that he/she will take on their basis, will substantially improve their patient's life" [47]. This statement further supports the use of discrete testing over biochemical profiling in our efforts to diagnose early disease.

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