The Side Effects of Translational Omics: Overtesting, Overdiagnosis and Overtreatment

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Conflict of Interest

• We declare (scream) no conflict of interest with this presentation
Goals and Objectives

• Not to bash new technology
• Not to “resist” progress
• Not to antagonize “Pioneers”

But
• To balance the enthusiasm with the seemingly obvious huge gains with NEW OMICS TESTING, by also explaining and discussing the possible associated limitations and harms
• Not many people are talking about these limitations

Published Work

This presentation is based on two recent papers by Dr. E. P. Diamandis
The hundred person wellness project and Google’s baseline study: Medical revolution or unnecessary and potentially harmful over-testing?
BMC Medicine 2015;13:5

The side effects of translational omics: Overtesting, overdiagnosis and overtreatment
Mol Cell Proteomics (under review)

Question to audience

• What is your preference to this statement?
• You are healthy until proven otherwise
• (no testing needed unless you feel unhealthy)
  Or
• You are sick until proven otherwise
• (must do a lot of testing to exclude occult disease)
Mark Cuban’s Advice on Twitter

• Have your blood tested for everything available every 3 months

• What a moron!

The Range of Diagnostic Tests in Rapidly Increasing Technology-Driven Trend

• Whole Genome Sequencing

• Deep RNA Sequencing

• Global Proteomic Analyses

• All sorts of portable micro-devices

The Decreasing Cost of Genotype Information: Genotype First?

[Graph showing decreasing cost of genotype information]
Perception/ Expectation of Many New Initiatives

• Identify early disease signs or disease predisposition (by testing at asymptomatic stage)
• Then, apply aggressive therapeutic or preventive measures to cure, slow down or avoid disease
• In this session we will examine:
  • Does this approach work? What is the evidence based on previous experiences?

Definitions

• What is Over-Testing?
  • Testing that you do because you can, not because is useful
  • Testing that does not lead to an action that will help the patient
  • Example: a millionaire does weekly MRI testing to detect possible early brain tumour development

What is Overdiagnosis?

Diagnosis of a disease that would otherwise never become clinically apparent (never cause symptoms or death during a patient’s lifetime)


Example: Identify by screening, a small, low-grade prostate cancer in an 80 year old man
What is Over-Treatment

• The consequence of Over-Diagnosis

• Treat a disease that would otherwise never become clinically apparent (never cause symptoms or death during a patient’s lifetime)

• Example: Radical prostatectomy in an 80 year old man with low grade prostate cancer

Incidental Findings

• Findings unveiled during testing for something else

• Not necessarily a bad thing; it may save your life at times, but it may also lead to an unnecessary treatment

• Such findings are becoming very common with Next Generation Sequencing test

Indolent disease

• a disease that would otherwise never become clinically apparent (never cause symptoms or death during a patient’s lifetime)

• You do not want to find such disease because it may lead to over-treatment

• Example: 80% of dead men have microfoci of prostate cancer at autopsy
Current Trend—The “Big Thing”

- Testing asymptomatic individuals
- This is equivalent to “population screening”
- With inexpensive and easy access to the information running through their veins, people will have an unprecedented window on their own health. A new generation of diagnostic tests could allow them to head off serious afflictions from cancer, to diabetes, to heart disease
- Elisabeth Holmes, Theranos CEO, a company that markets self-testing
- in pharmacies

Future Projections

Leroy Hood says that in the near future, with a drop of blood, we will be able to quantify thousands of proteins and assess function or disease of all organs in our body.

Check your health as frequently as you check your email!
Some High-Profile Wellness Projects that have just been initiated

Google’s Baseline Study

• Google Seeks Human Guinea Pigs for Health Project
  • http://time.com/3045429/google-baseline-study-human-health

• The project will collect hundreds of samples, and then find “biomarkers,” or patterns, within the data. Scientists hope these biomarkers will help them detect disease much sooner, or tell them which kinds of biological conditions make someone a likely candidate for e.g. high cholesterol.

Google’s "Baseline Study" aims to get clear picture of human health

• Google wants to collect a staggering amount of information about each of its anonymous human guinea pigs. They’re mapping each person’s entire genome, and their parents’, not to mention looking at how they metabolize food, and how their hearts beat, and their oxygen levels. Participants will even wear special smart contact lenses so Google can monitor their glucose levels.
Google is developing cancer and heart attack detector


- Google is aiming to diagnose cancers, impending heart attacks or strokes and other diseases, at a much earlier stage than is currently possible.

- The company is working on technology that combines disease-detecting nanoparticles, which would enter a patient’s bloodstream via a swallowed pill, with a wrist-worn sensor.

- The idea is to identify slight changes in the person’s biochemistry that could act as an early warning system.

NIH Plots Million-Person Mega-Study

- Convince 1 million Americans to wear smart watches that beam their blood pressure, steps walked, and other health information to a central database every hour of every day?

Science 2015;347:817

The 100 Person Wellness Project

Nature 2014; 506:144
Point/Counterpoint

• Will such strategies improve health or lead to overtesting/overdiagnosis/overtreatment?

  Integrating big data and actionable health coaching to optimize wellness.
  Hood L, Lovejoy JC, Price ND.

  The Hundred Person Wellness Project and Google’s Baseline Study: medical revolution or unnecessary and potentially harmful over-testing?
  Diamandis EP.

Lake Nona Life Project


• Lake Nona is embarking on a multi-generational study focused on community health and wellness. Residents and those who work in lake Nona will have the unique opportunity to participate in this place-based study that seeks to better understand the factors determining our overall well-being.

Theranos

Elisabeth Holmes
Young Billionaire Executive
Best 30 under 30
$9 Billion Company valuation
BUSINESS MODEL

“Our mission is to make actionable health information accessible to people everywhere in the world at the time it matters, enabling early detection and intervention of disease, and empowering individuals with information to live the lives they want to live.”

• CHEAP
• QUICK – RESULTS IN <4 HOURS
• PAINLESS – FINGER STICK
• FRUGAL – “Nanotainer” 25-50 uL - Any analyte from the same sample (70 tests)
• ACCESSIBLE – WITHIN 5 MILES
• LARGE MENU – 200 TESTS (or flex)
• FDA – “SUBMIT ALL OUR TESTS…”
• CUSTOMERS – Walgreens Wellness Centers (41 so far), PHARMA (PFIZER, GSK), Military, Hospitals (Cleveland Clinic, Dignity Health)
• GROWTH GOAL – 1 million tests by 2015

And: Ioannidis J. JAMA 2015;313:663-4

Theranos

Results to patients
Self-testing and self interpretation

Cancer screening:
Less is more?

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Population Screening

- Testing of asymptomatic individuals to detect occult disease

- We will now examine:
  - the accepted criteria of screening
  - screening experiences and lessons learned, over the last 40 years

Accepted Criteria for Screening

(Wilson and Junger, 1968)

- The condition should be an important problem with a known natural history
- Have an agreed policy on whom to treat
- Diagnostic and treatment facilities are available
- There should be a suitable, acceptable test
- The cost of case-finding should be economically balanced in relation to medical costs as a whole

- These testing criteria should also be considered when new Omics technologies are intended for testing asymptomatic individuals to identify preclinical disease

Successful Experiences from Existing Screening Programs

- Neonatal screening for Phenylketonuria and Congenital Hypothyroidism
- Prenatal screening for Down Syndrome and other trisomies

Current neonatal screening with mass spectrometry covers approx. 50 rare disorders
A recognized issue with even established screening programs

- Screening may uncover not only clinically significant cases which can benefit from early treatments

- But

- Sometimes larger number of cases who are asymptomatic

Such positive results 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

Wilcken B. Science 2013;342:197-8

Whole Genome/Exome Sequencing and Deep RNA Sequencing

- All newly proposed wellness studies suggest sequencing of the genome of all participants

- Why?

- To find pathogenic mutations (occult disease) or mutations that are associated with future disease predisposition (for possible prevention)

The $1,000 Genome is Here

- Assuming it’s running at full capacity and including all costs—the purchase price, plus labor and reagents—the Illumina machine can sequence an entire genome for:

$1000
Issues with Whole Genome Sequencing

Technical Issues

• Read accuracy
  Human genome: 3 billion bp
  Current technology accuracy: 1 false SNV per 1,000,000 bases
  = 3,000 false SNVs

• How could you find out which variations are real and which variations are false positives?

• Independed verification is expensive

Quality Assurance

• Platform-specific variability (improving)

• Technical/interpretative standards are still emerging

• Regulatory organizations to monitor quality are still emerging (CAP; ACMG)

• Impact of ethnicity (rare variants)
Next Gen Sequencing

Major issues
• Must verify positives to exclude false positives
• How to identify pathogenic from non-pathogenic mutations
• How to report incidental findings
• Genotype may not significantly affect phenotype

Most important problem with Next Generation Sequencing

The discovery of rare genetic variants is accelerating, and clear guidelines for distinguishing disease-causing and non-disease causing variants are urgently needed.

Without rigorous standards we risk an acceleration of false-positive reports of causality, which would impede the translation of genomic research findings and hinder biological understanding of disease.

• Incidental finding: unexpected positive findings
• Constitutional mutations found in the genes on the minimum list should be reported by the laboratory to the ordering clinician, regardless of the indication for sequencing
• It is the responsibility of the ordering clinician to provide comprehensive pre- and posttest counseling to the patient

CLARIFICATION 2014
 Patients can choose to opt-out of learning about incidental findings after consultation with counsellor
• Assessed the capacity of whole-genome sequencing to identify individuals at clinically significant risk for 24 different diseases:
  – For 23 of the 24 diseases, the majority of individuals will receive negative test results.
  – These negative test results will not be very informative, as the risk of developing 19 of the 24 diseases in those who test negative will still be 50 - 80% of that in the general population.
  – More than 90% of tested individuals might be alerted to a clinically significant predisposition to at least one disease.

• Analysis of 406 published severe disease mutations: 122 (27%) of these were either common polymorphisms or lacked direct evidence for pathogenicity

• Numerous alleged severe-disease-causing variants were found in the genomes of population controls

• Well-powered follow-up validation studies have cast serious doubts on initial reports

Association vs. Causality!

• Analysis of 406 published severe disease mutations: 122 (27%) of these were either common polymorphisms or lacked direct evidence for pathogenicity

• Numerous alleged severe-disease-causing variants were found in the genomes of population controls

• Well-powered follow-up validation studies have cast serious doubts on initial reports

• Provide complete positive and negative evidence, not just the results that are consistent with pathogenicity.

• Do not regard prior reports of gene or variant implication as definitive

• Apply statistical methods to compare the distribution of variants in patients with large matched control cohorts

• Recognize that strong evidence that a variant is deleterious or damaging is not sufficient to implicate a variant as playing a causal role in disease.
Disease prevalence: 1: 100,000

- A test with:
  - 99.9% sensitivity
  - 99.9% specificity

- If you screen 10,000,000:
  - 100 will have the disease
  - 10,000 will be false positives
  - 100 patients will be missed

Genomic measurements is likely to yield unexpected incidental findings for nearly everyone.

Patients will be subjected to unnecessary follow-up tests, causing additional morbidity.

The cost of genomic medicine will increase substantially with little benefit to patients.

• Their value remains a subject of vibrant debate

• Oncologists are expected to encounter increased patient requests for genetic tests or requests for advice

• All lead to: lifestyle changes, common advice like eating vegetables

• Side effects:
  - No significant behavioral changes happened
  - No anxiety (unexpected)
  - Fatalism
Whole Genome Sequencing
(even if 100% accurate)

• May not accurately predict disease risk (for most diseases environmental factors are more dominant)

• Variants of unknown significance (Incidentalomas)

• If you do WGS now, for disease prevention, you may get more confused than enlightened since interpretative standards are still emerging

Issues with biochemical profiling strategies

Disease Screening by Biochemical Profiling– Something New?

• The concept of biochemical profiling for asymptomatic disease detection is not new!

• How many of you are old enough to remember the Technicon SMAC Analyzer? (1970s)

• Could measure 80 analytes simultaneously!

Biochemical Profiling vs. Discrete Testing

• Biochemical profiling will have approx. 5% false positive results (test results outside the reference intervals in otherwise normal subjects)

• This is due to the definition of reference intervals; i.e. 2.5-97.5 percentile of a reference population

Biochemical Profiling vs. Discrete Testing

• High cost of investigating seemingly abnormal results in normal people let to the complete replacement of biochemical profiling with “discrete” testing i.e tests are performed only if specifically requested by the physician

• Lesson: multianalyte testing will yield false positive results in a small (i.e 5%) of normal individuals, leading to additional unnecessary investigations and probably harmful interventions

Cancer Screening: Effective?
Cancer Screening Premise

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

Screening Caveats

• Even if the screening method is highly sensitive and specific, if disease prevalence is low, the predictive value of the test will be LOW! (meaning too many false positives)

• Separating false positives from true positives may not be trivial, and could lead to potentially harmful procedures such as biopsies, laparotomies and surgeries!

• Screening may uncover indolent disease, leading to over-treatment
Effect of Prevalence of Disease on PPV and NPV

• For a test with 95% diagnostic sensitivity and 95% diagnostic specificity

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<th>Disease prevalence, %</th>
<th>PPV of pos. test result, %</th>
<th>NPV of neg. test result, %</th>
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Cervical Cancer-Screening Success

• Cytological screening every 3 years or combined cytological and HPV-cotesting every 5 years

MORTALITY RATES


Canadian Recommendations

• For women aged < 20 we recommend not routinely screening for cervical cancer.
  (Strong recommendation; high quality evidence)
• For women aged 20 to 24 we recommend not routinely screening for cervical cancer.
  (Weak recommendation; moderate quality evidence)
• For women aged 25 to 29 we recommend routine screening for cervical cancer every 3 years.
  (Weak recommendation; moderate quality evidence)
• For women aged 30 to 69 we recommend routine screening for cervical cancer every 3 years.
  (Strong recommendation; high quality evidence)
• For women aged ≥ 70 who have been adequately screened (i.e., 3 successive negative Pap tests in the last 10 years), we recommend that routine screening may cease. For women aged 70 or over who have not been adequately screened we recommend continued screening until 3 negative test results have been obtained.
  (Weak recommendation; low quality evidence)
Colon Cancer - Favourable Data

- Screening for colon cancer reduces the disease-specific death rate by approx. 30%
- Colonoscopy-based screening carries a complication rate of 0.1%, including colon perforation and bleeding


Canadian colorectal cancer screening recommendations

- The Canadian Cancer Society recommends that men and women age 50 and over have a stool test (guaiac-based fecal occult blood test or fecal immunochemical test) at least every 2 years. There is convincing evidence that stool tests with appropriate follow-up can significantly reduce deaths from colorectal cancer.
- Follow-up for a positive test should include a colonoscopy or double contrast barium enema (an x-ray of the large intestine) or flexible sigmoidoscopy.
- This recommendation applies only to people who are at average risk of developing colorectal cancer. People who have a first-degree relative with colorectal cancer, personal history of colorectal cancer, inflammatory bowel disease, some inherited syndromes or benign polyps should develop an individualized plan of surveillance with their doctors.

Breast Cancer

- 30 years experience
- 30% decrease in death rates attributed more to improved therapies rather than screening
- Screening increases breast cancers detected from 112 (no screening) to 234 cases per 100,000 women screened but late stage cancers decreased from 102 (not screened) to 94 (screened) per 100,000 women

- What is the explanation?
Explanation

• Breast cancer screening DOES NOT significantly decrease rates of late stage cancers (no stage migration)

Because such cancers develop and grow quickly (missed in one round of screening and detected as late stage in subsequent round)

The majority of additional cancers detected, are likely those that are slow-growing and do not progress to advanced disease (overdiagnosis)

Estimated magnitude of Overdiagnosis

• Tumors detected by screening that would have never led to clinical symptoms
• 1.3 million over last 30 years!

• Should breast cancer screening be abolished?

Harms and Benefits of Mammographic Screening

Benefits: per 1,000 women screened
1 breast cancer death prevented over a 10-year course of annual screening, starting at age 50

Harms:
• 490 - 670 women are likely to have a false positive mammogram with repeat examination
• 70 - 100 women will undergo an unnecessary biopsy
• 3 - 14 women will have an over diagnosed breast cancer

Canadian Guidelines

• **Recommendations (Mammography)**
  • For women aged 40–49 we recommend not routinely screening with mammography.
    *(Weak recommendation; moderate quality evidence)*
  • For women aged 50–69 we recommend routinely screening with mammography every 2 to 3 years.
    *(Weak recommendation; moderate quality evidence)*
  • For women aged 70–74 we recommend routinely screening with mammography every 2 to 3 years.
    *(Weak recommendation; low quality evidence)*
Lung Cancer Screening
(low dose computed tomography)

• Reduces mortality by about 20% in heavy smokers

• This screening is associated with many false positives, incidental findings and exposure to radiation

• 95% of positive results do not lead to lung cancer diagnosis

• Unnecessary invasive diagnostic procedures in 1-4% of screened population

• 25% of surgical procedures done yielded benign pathologies


USPSTF Recommendations

The USPSTF recommends annual screening for lung cancer with low-dose computed tomography (LDCT) in adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery.

The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.

Ovarian Cancer Screening

• Effect of screening on mortality is unknown

• Predictive value of available tests are low (3-30%)

• Thus, for confirmation, more women without ovarian cancer will undergo laparotomy than women with ovarian cancer

• The USPSTF recommends against screening for ovarian cancer in women.

Prostate Cancer

• Prospective randomized trials have shown that

• Incidence increases significantly

• Modest decrease in prostate cancer-specific death (20%) with screening, at the expense of diagnosing a lot more patients, performing many unnecessary biopsies and treating slow-growing tumors

• The U.S. Preventive Services Task Force (USPSTF) recommends against prostate-specific antigen (PSA)-based screening for prostate cancer.

Less is More?

• Breast Cancer
• Lumpectomy and total mastectomy for breast cancer do not differ in outcome

• Prostate Cancer
• Small differences in overall mortality in men who underwent radical prostatectomy (47%) and men who were randomized for observation (50%)

Active Surveillance

• New grading system for CaP- Five level grading

• Group 1(3+3=6)
• Group 2(3+4=7)
• Group 3(4+3=7)
• Group 4 (Gleason 8)
• Group 5 (Gleason 9 and 10)

• In USA only 10% of patients are on active surveillance vs 50% in Canada
• Men 55 or older with favourable disease (Gleason 6) active surveillance is a safe management option over at least 10-15 years
Escape from Cure
• The point at which a cancer ceases to be curable

The concept of “Escape From Cure”. Data are based on the PIVOT trial. For patients with localized prostate cancer, patients with a PSA ≤ 10ng/mL at diagnosis had similar overall mortality whether treated by radical prostatectomy (46%) or observation (44%). Beyond the “Escape From Cure” point (PSA > 10ng/mL), the overall mortality was superior with radical prostatectomy (48%) versus observation (62%).

Question
• With some exceptions (pregnancy; blood glucose etc)

• Is it a good idea to have asymptomatic individuals test themselves, interpret results and take action?

• What action?
Another “World’s First” (February 2015)

FDA allowed 23andMe to market a test for mutations that cause a rare disease called Bloom Syndrome

This was the first time that the agency had approved a genetic test marketed to the public, not clinicians

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Conclusions

- More aggressive treatments are not always better than less aggressive treatments
- Early diagnosis may not always lead to better outcomes
- Overzealous testing, done due to technical advances, may or may not be useful
- In some cases, excessive testing could harm the patient
- With wellness/asymptomatic individual testing, the benefits and harms need to be carefully considered
“Less is More” Movement

- Considered the “Next big thing in Medicine”
- Reduce screening
- Reduce low value diagnostic tests
- Reduce low value treatments
- The above have potential for more harm than good

“Choosing Wisely” Campaign

- Launched in 2012 by the American Board of Internal medicine
- Name an evidence-based top 5 list of tests and procedures that physicians and patients should question because they offer little or no benefit and may cause harm
- As of today, more than 70 specialty societies have joined the campaign
I will not request an investigation unless I am confident that the answer, and the actions I take on its basis, will substantially improve my patient’s life.

**Suggestion for Over-Testing**

To the Hippocratic Oath might be added:

I will not request an investigation unless I am confident that the answer, and the actions I take on its basis, will substantially improve my patient’s life.

**THE LANCET** 2012; 380: 307

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**Major Journals and Conferences**

- JAMA Internal Medicine “Less is more” series
- British Medical Journal “Too much medicine” campaign
- Annual Conferences: Preventing Overdiagnosis