Next Generation Sequencing in Clinical Practice: Current Status and Future Needs

Kathryn A. Phillips, PhD
Professor of Health Economics, Dept Clinical Pharmacy, UCSF
Founding Director, Center for Translational and Policy Research on Personalized Medicine (TRANSERS)
Today: Key Takeaways

• NGS tests becoming available globally – but need data & evidence on how implemented
• Increased US payer coverage for some tests - but coverage variability
• Evidence of economic value emerging - but mixed results & methodological challenges
• Emerging tests for population screening – seismic shifts for coverage, costs, access, disparities!
• Emerging payer and lab models – seismic shifts for coverage, costs, access, disparities!
• What does the future hold?
1) The largest numbers of tests and expenditures by US commercial payers are for tumor sequencing tests.

2) “Liquid biopsy” tests for early cancer detection will not be available in the clinic for several years.

3) Access to hereditary cancer panel testing via safety net clinics is decreasing.

4) Muin tweets rather than sleeps.
1) The largest numbers of tests and expenditures by US commercial payers are for tumor sequencing tests
False
- Largest numbers of tests are prenatal tests, e.g., NIPT
  E.g., Among commercial payers in 2019, 500K NIPT tests vs. 70K tumor sequencing tests
- Largest expenditures are for prenatal tests and cancer germline tests
  But tumor sequencing tests are some of the highest cost tests
  FoundationOne CDx = $3500 Medicare reimbursement rate, $5700 list price

2) Liquid biopsy” tests for early cancer detection will not be available in the clinic for several years
Appears to be false. At least one company plans to selectively market their test in 2021

3) Access to hereditary cancer panel testing via safety net clinics is decreasing
Appears to be false. Our findings from two studies suggest that many labs are providing free or low cost testing and thus costs are less of a barrier.
  - However, genetic counseling is still a barrier and the pandemic may change this.

4) Muin tweets rather than sleeps
Appears to be true. 3233 followers.
TRANSPIRES
A Decade of Providing *Objective* Evidence on Value & Reimbursement

- Focus on *solutions* for challenges of reimbursement, economic value, and adoption
- Funded by NIH and foundation grants
  - Initially funded via NIH P01 Program Project Grant
  - Continuous NIH funding through multiple grants
- 100+ publications

Center for Translational and Policy Research on Personalized Medicine
University of California, San Francisco
TRANSVERS is interdisciplinary
TRANSPERS is **Integrated Across Stakeholders**
NGS tests becoming available globally – but need data and evidence on how implemented
Clinical Genomic Sequencing Tests Becoming More Widely Available Globally

Dark Blue = Availability of:
- whole exome sequencing
- non-invasive prenatal testing
- tumor sequencing

Medium Blue = 2 of 3 tests available

Light blue = 1 of 3 tests available

Phillips et al 2020
<table>
<thead>
<tr>
<th>Implementation Factors</th>
<th>Data Gaps</th>
<th>Possible Data Sources</th>
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| **Availability of NGS Tests for Clinical Use** | - No source for availability worldwide or across clinical applications  
- Limited and/or outdated information on many countries | Published journal articles  
Gray literature and Online News (e.g., GenomeWeb)  
Administrative and clinical data (e.g., NIH Genetic Testing Registry) |
| **Utilization (# tests ordered)** | - No source for utilization worldwide or across clinical applications  
- Limited data except US populations in specific health plans or centers | Published journal articles  
Gray literature (e.g., Market reports such as investor analyses)  
Administrative and clinical data (e.g., White papers, such as Personalized Medicine Coalition 2020 report) |
| **Funding** | - No source for funding worldwide or across clinical applications  
- Some data available on government programs and US private payer or Medicare coverage  
- Limited data on many countries, regional coverage, and Medicaid coverage | Published journal articles  
Gray literature (e.g. Advocacy group such as Coalition for Access to Prenatal Screening)  
Administrative and clinical data (e.g., proprietary databases such as Canary Insights) |

Gray literature = white papers, health system reports, market analyses, regulatory filings, company websites, news reports, national/international consortia websites  
Administrative and clinical data = electronic health records, claims data, fee schedules, industry databases, registries
“Data More Important than Oil”
Jack Ma, Alibaba Group

“In God We Trust, All Others Bring Data”
Joe Newhouse, Harvard

Artificial Intelligence, Machine Learning, Data Science, Big Data, Real World Evidence

- Such “hot” topics that NHGRI gave me special senior career award to figure out implications for Precision Medicine
New Results: Applying Machine Learning to Precision Medicine

- Assessing implementation requires use of real-world data (RWD)
  - But long-standing challenges

- We examined how RWD has been used in studies of precision medicine utilization, assess challenges in using RWD, and discuss possible machine learning solutions
  - Found that RWD is being used, but none of the identified studies used machine learning – even though could potentially address commonly cited challenges

### Percentage of Studies by Characteristics (N=39)

<table>
<thead>
<tr>
<th>RWD Type</th>
<th>Integrated Dataset</th>
<th>Data Challenges Noted*</th>
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</thead>
<tbody>
<tr>
<td>Administrative Commercial</td>
<td>33%</td>
<td>33%</td>
</tr>
<tr>
<td>Administrative Public</td>
<td>26%</td>
<td>95%</td>
</tr>
<tr>
<td>Clinical</td>
<td>21%</td>
<td>46%</td>
</tr>
<tr>
<td>Lab</td>
<td>18%</td>
<td>35%</td>
</tr>
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*Percentages add up to >100% because studies may have used more than one data source or noted more than one challenge.
Increased US payer coverage for some tests - but coverage variability
Sum Greater Than the Parts: Our Multi-Methods Approach to Understanding Coverage

Systematic analyses of published coverage policies

In-depth descriptive studies of payer perspectives
2007: Established Payer Advisory Board
Senior executives from largest private health plans; Leading regional plans; Medicaid; Thought leaders

In-depth descriptive studies of providers of genetic testing

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Rise of Large Gene Panels Creates Dilemmas for Payers

• Payers’ Mandate: “medically necessary & not experimental”
  - Assumes testing for one marker, one reason, and intervention based on results
  - All genes measured must have clinical utility

• Blurring of research vs. clinical use

• Slippery slope of population-wide screening vs. targeted testing

• Personal utility of results vs. clinical outcomes

• Concerns that lack needed delivery systems & that patients/clinicians lack understanding of appropriate use and interpretation

• Inability to track utilization because of lack of precise coding
Increasing Coverage for Some Tests & Payers

Non-Invasive Prenatal Testing for high-risk women – fastest adopted and covered test in history
  - But ongoing debate about coverage for average risk women

Increased coverage of NGS: cancer germline panels, exome sequencing for infants in NICU and for rare and undiagnosed diseases in children

Variable coverage:
  - Testing for drug metabolism, cardiovascular, expanded carrier screening
  - Testing across Medicaid programs and w/in Medicare regions/regional vs. national

Interesting discrepancies between available tests via direct-to-consumer labs vs. what is covered/recommended
  - APOE testing for late onset dementia offered by 23andMe & Helix received FDA clearance for Health Risk App for APOE (Feb 2021)
    - But not clinically recommended or covered by payers
Illustration of Opportunities & Challenges:
2018/2020 CMS National Coverage Decision on Advanced Cancer Sequencing

Suspense
Politics
Economic implications
Industry implications
Access implications

Sources: Phillips et al, JAMA 2018 & Phillips et al, Science 2018
“Like it or not, new CMS policy aims to change everything in next generation sequencing”

- Paradigm shift in coverage approach w/ ripple effects with other payers & tests
  - Coverage for companion diagnostics (only)
  - FDA approval/clearance required for automatic coverage
  - If one gene meets requirements, entire panel is covered

- Challenges
  - Does not provide for coverage of lab-developed tests - left up to MACs
  - Pathway to coverage via Coverage with Evidence Development removed
  - Confusion & later revision: inadvertently blocked coverage of germline risk testing
  - Not all private payers following suit
  - Medicaid access?
  - No assessment of impact on costs

Sources: Phillips et al, JAMA 2018 & Phillips et al, Science 2018
Circulating tumor DNA (ctDNA) testing to select targeted therapy and monitor non-responding or progressive tumors for cancer has rapidly emerged into clinical care

- But no previous studies of payer coverage

Why important

- Less invasive than tumor biopsies and can be used when tissue not available (e.g., lung cancer)
- Ability to easily monitor response to therapeutic agents
- May pave the way towards use of tests for early cancer detection

Source: Douglas, Gray, Phillips, JNCCN, 2020
Results:
Rapid Increase in Coverage
2015-2019

Private Payers:
0% to 38% Coverage

Medicare Local Coverage Determinations:
0 to 12 LCDs (10 final, 2 draft)
Majority of positive policies for lung cancer only BUT several new Medicare Local Coverage Determinations are pan-cancer

Percentage of Private Payer Policies with Positive vs. Negative Coverage

73 POLICIES FROM 200 PAYERS

Positive 38%

Negative 62%

Percentage of Positive Policies By Specific Characteristics (N = 73)

- NSCLC ONLY: 86%
- BRANDNAME ONLY: 79%
- EGFR ONLY: 4%
- PAN-CANCER: 14%
- MONITORING: 11%

Medicare: 4 LCDs provide pan-cancer coverage for 12 solid tumors

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Whole Genome or Whole Exome Sequencing?
Benefits, Challenges and Potential Path to Coverage

Summary of Preliminary Findings

Part of a cross-institutional study within the NIH CSER program grant

CSER: The Clinical Sequencing Evidence-Generating Research Consortium
Webinar participants

TRANS磷ERS Payer Advisory Board (in alpha order)
• Virginia Calega, MD, Independence BlueCross*
• Patrick Courneya, MD, HealthPartners
• David Haddad, MD, Health Net
• Shauna Hay, MPH, Beacon
• Erick Lin, MD, PhD, BlueCross BlueShield Association*
• Brian Loy, MD, Humana
• Bruce Quinn, MD, PhD, MBA, Bruce Quinn Associates
• Kim Reed, MD, MBA, JD, Health Care Service Corporation
• Emily Tsiao, PharmD, Premera BlueCross
• John Watkins, PharmD, Premera BlueCross
• John Whitney, MD, Anthem
• (to be interviewed separately: Jen Malin UHC, Joanne Armstrong Aetna, Alison Martinez Oklahoma Medicaid*)

CSER site project participants
• Hadley Stevens Smith, Baylor College
• Bruce Gelb, NYCKidSeq
• Veronica Greve, HudsonAlpha Inst of Biotech
• Anne Slavotinek, UCSF
• Beth Devine, Univ of Washington

National Human Genome Research Inst
• Lucia Hindorff, Ph.D., M.P.H. NHGRI, Program Official

UCSF TRANS磷ERS
• Kathryn Phillips
• Michael Douglas
• Julia Trosman
• Christine Weldon

*Former
Webinar Format and Agenda

1. TRANSPERS Team provided background on differences between WGS and WES pertaining to insurance coverage
   - Background materials were also emailed prior to webinar

2. Discussion was facilitated along three aspects:
   a) Benefits of WGS vs. WES in the context of insurance coverage
   b) Challenges & concerns about WGS vs. WES related to insurance coverage
   c) Potential path to insurance coverage of WGS / WES
Results: Payers’ feedback on benefits of WGS vs. WES

• Regarding perceived higher accuracy and lower variability
  • Payers want evidence that (a) WGS is in fact superior to WES in these two aspects (b) that this is clinically significant

• Skeptical about “diagnostic” yield difference b/w WGS and WES
  • Better to call this “genetic difference” – it’s a leap from genetic finding to diagnosis or clinical outcome

• Replacing WES+CMA with WGS
  • Payers need to know if WGS can fully replace WES+CMA – will providers do WES+CMA and then WGS? Will they need to stop coverage of WES+CMA?

• “Trending positive” on both WGS and WES; but question broad use as still premature

• Ending diagnostic odyssey: need to know its value
Results - Payers’ feedback on concerns / challenges related to WGS vs. WES

• Cost
  • Consideration for insurance coverage for some payers, but not for others
  • Payers could model costs based on claims data to compare costs WGS and WES+CMA
  • Expect cost to come down with broader adoption in community

• Varying quality across labs – a big concern
  • Different criteria classification systems, levels of adherence to ACMG guidelines
  • Lack of transparency

• Variants of unknown significance
  • Some concerned that higher rate of VUS with WGS will explode costs
  • Others not concerned: have policies for VUS already

• Concern the average provider would not understand the difference between WGS vs. WES, and when to order one vs. another
Results - Payers’ thoughts on path toward potential insurance coverage of WGS

• Coverage should come with a requirement for registry to learn from real-world use
  • For VUS and outcomes
  • Important for future retesting

• Evidence needed
  • Need evidence of WGS benefit in specific clinical scenarios – then could be covered only for those scenarios
  • Some payers: should develop “real evidence”, not ”real world” evidence

• Intermediate or clinical outcomes?
  • Better to have direct clinical outcomes than intermediate outcomes
  • When rare or long-term course disease, intermediate outcomes may suffice; then need the timeframe and a “link” from intermediate to clinical outcomes

• Must have quality standards and transparency of lab methods and quality
  • Could manage this via contracting and networks, if standards exist
Results - Payers’ thoughts on path toward potential insurance coverage of WGS, Cont’d

• Coverage with evidence development (CED)
  • Some perceive this as research – not the role of payers; employers don’t support paying for this
  • However, CED may have a role in value-based contracts, to identify relevant patient populations

• Must incorporate the role of genetic counselors (for non-ICU settings) to ensure appropriate use

• Clinical center of excellence
  • If concrete criteria of excellence could be identified:
    • Capacity to collect real-world data; best practices (e.g., genetic counseling, shared decision making), standard clinical protocols, etc.

• Payers saw value in potential coverage for WGS in pediatric populations, but not in adult populations

• *No clear / single reason why WGS not covered as much as WES
  • Threshold needs to be reached of combination of things, e.g., head-to-head evidence, same cost for both, confidence that interpretation is standard
  • When these things come together enough, they will cover it – when it becomes “standard of care”.
Evidence of economic value emerging - but mixed results & methodological challenges
Some Studies Show Economic Value of Precision Medicine – But Still Large Gaps

• Some studies find genetic testing to be cost-effective relative to usual care
  – But difficult to define and measure economic value in appropriate, comprehensive way
  – Not usually “cost-saving” – but few health care interventions are

• Global Economics and Evaluation of Clinical Sequencing Working Group (GEECS) formed to address methodological issues
  – Published several journal themed issues – but still working on solving the challenges
Solicited paper for *Science* special issue: *Should We Focus on Affordability or Value of Precision Medicine? We Need Both*

**Affordability** = Can we pay for it? (budget impact)

**Value** = Should we pay for it? (cost-effectiveness analysis)

Special issue Feb 4: 20th anniversary of *Science* and *Nature* publishing the human genomes

- Previous 10th anniversary issue: articles by Francis Collins, Craig Venter, Bruce Alberts
- Solicited to write perspective on economics (included two new more junior colleagues)
- Other articles on big data, diverse populations, data sharing, privacy

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Affordability or Value?
- Often conflated then wrong questions or wrong answers

Evidence suggests PM is often affordable and a “good value”
• Challenges:
  • Lack of data
  • Need to consider special issues for inherited conditions
  • Increasing use of PM for population screening may incur large up-front expenditures even if also paradigm-shifting benefits, e.g., Liquid biopsy for cancer screening, predictive testing for Alzheimer’s disease in adults with mild cognitive impairment

Solutions? Examine both affordability and value at same time
• Usually done independently
• US policymakers now showing willingness to consider both
  E.g., ICER’s work on pharmaceuticals incorporates both and is having large influence on industry and payers
Emerging tests for population screening – seismic shifts for coverage, costs, access, disparities!
Proposal Under Council Review: Building Evidence Base for Appropriate & Efficient Implementation of Emerging Genomic Tests For Disease Management & Screening

• **Objective:** Assess payer coverage decisions and economic value of two types of emerging genomic tests for disease management and screening:
  • Cell-free DNA tests, e.g., liquid biopsy for cancer screening
  • Tests using polygenic risk scores, e.g., predictive algorithms for CVD risk

• Illustrates opportunities and challenges as PM moves from targeted testing to *population screening*, using *less-transparent/more complex methods*

• **Questions:**
  • What is covered by payers? Why? What evidence is required?
  • What is economic value? How do we measure it?
  • How do we take into account impact on disparities? Diverse stakeholders? Changing health care system?
Study Framework

Study Overview: Evidence Needed for Appropriate/Efficient Implementation

Aim 1: PAYER COVERAGE
- What is covered by payers & why?
- What evidence needed for coverage?

Aim 2: ECONOMIC VALUE
- What is the economic value of the test?
- What methods are most appropriate?
- What evidence is needed for assessing economic value?

Clinical Scenarios

Application
- Disease Management
- Screening

Technology
- Cell-Free DNA Tests
- Polygenic Risk Scores

Condition
- Cancer
- Other Conditions

Impact on Patient Access & Disparities

Evolving Healthcare Ecosystem & Stakeholder Perspectives

Aim 3: EVIDENCE NEEDS AND GENERALIZABILITY IN OTHER CLINICAL SCENARIOS
10 Breakthrough Technologies: Liquid Biopsy

Fast sequencing machines leading to simple blood test for cancer.

• Has potential benefits
  – Earlier detection, non-invasive, may be rapid/accurate/less expensive

• But many questions
  – Accuracy/validity, benefits vs. harms of earlier detection, substitute or complement?
  – Will payers cover given that population screening?
  – Could upend traditional cancer screening model by cancer type

• Illustrates complexities of assessing economic value
  – Multiple pathways of events and probabilities
  – Complex data inputs needed
  – Role of patient and provider preferences
Liquid Biopsy for Cancer Screening: Example of Emerging Trend of Precision “Health”

- *Precision Health* leverages omics, immune status, medical imaging, family history, physical condition and standard doctor visits to predict and prevent disease from occurring.

- Complicated....
  - Which predicted risks for which diseases should be considered for which individuals and when?
  - What interventions? To whom?
  - Who should pay?
Evolving payer & lab models – seismic shifts for coverage, costs, access, disparities!
Seismic Shifts in Payers & Lab Industry

- Emergence of low-cost testing via “hybrid labs”
- DTC testing obsolete?
- Disparities in access decrease – but sustainable?
- Emergence of lab benefit managers & preauthorization companies
- Payers no longer at nexus of decision-making?
- Patients able to obtain appropriate testing?
Can Precision Medicine Reduce Disparities in Access to Care and Health Outcomes?

• Work focusing on *structural* and *societal* factors and how precision medicine could reduce those

• Series of papers
  • Surprising changes in laboratory business models that are increasing access now but may, in the long run, reduce access and increase disparities
  • How new advances in methods for population screening (e.g., liquid biopsy, predictive testing for Alzheimer’s Disease) could increase vs. decrease disparities
  • Need to explicitly consider health equity in value frameworks and economic evaluations
  • That telehealth programs, which could reduce disparities, may not do so even when patients have no out-of-pocket costs
**TRANSPERS Study Shows Shift to “Hybrid” Labs**

- Historically, lab testing was clinician-centric
- Rise of DTC testing for health risks but concerns
- Thus, rise of consumer AND clinician-centric labs

<table>
<thead>
<tr>
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<th>DTC Model</th>
<th>Hybrid Model</th>
<th>Traditional Model</th>
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<tbody>
<tr>
<td><strong>Primary emphasis</strong></td>
<td>Consumer Access &amp; Information</td>
<td>Consumer Access &amp; Clinical Care</td>
<td>Clinical Care</td>
</tr>
<tr>
<td><strong>Central role</strong></td>
<td>Consumer</td>
<td>Consumer &amp; Clinician</td>
<td>Clinician</td>
</tr>
<tr>
<td><strong>Testing</strong></td>
<td>Limited</td>
<td>Broad</td>
<td>Broad</td>
</tr>
</tbody>
</table>

**Benefits:** access, convenience, cost, engagement  
**Risks:** quality, access, testing w/o counseling, continuity of care

Source: Phillips et al JAMA 2019
3 of 4 largest private insurers use LBMs to manage genetic testing
Range of functions from claims processing to writing draft coverage policies for payers
“Cumulative impact of LBM programs was “unprecedented” (Myriad Genetics)
Same trajectory as PBMs? Transparency? Impact?

Similar trend towards use of prior authorization companies

<table>
<thead>
<tr>
<th>Company</th>
<th>Date Founded</th>
<th>Ownership</th>
<th>Services Managed</th>
<th>Illustrative Contracted Health Plans</th>
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</thead>
<tbody>
<tr>
<td>AM Specialty Health</td>
<td>1999</td>
<td>Anthem (2)</td>
<td>Multiple (5)</td>
<td>- Anthem</td>
</tr>
<tr>
<td>Austin Healthcare Solutions</td>
<td>2013</td>
<td>Private</td>
<td>Lab only</td>
<td>- Multiple Blue Cross Blue Shield plans</td>
</tr>
<tr>
<td>Beacon Lab Benefit Solutions</td>
<td>2003</td>
<td>LabCorp</td>
<td>Lab only</td>
<td>- Unicare Healthcare</td>
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<tr>
<td>careCore</td>
<td>1994 (4)</td>
<td>Cigna (5)</td>
<td>Multiple (5)</td>
<td>- Multiple Blue Cross Blue Shield plans</td>
</tr>
<tr>
<td>Kastman Lab Benefit Management Program</td>
<td>2003</td>
<td>Private</td>
<td>Lab only</td>
<td>- Msp. plans (6)</td>
</tr>
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Access to Cancer Germline Testing has Increased for Safety Net Patients – But How Sustainable?

- Two interview-based studies
  - Providers in two states & AMC/Safety net
  - Lab experts

- Coverage and reimbursement challenges less prominent than in the past
  - External labs often subsidizing cost
  - Greatest challenge is lack of coverage for Medicare patients
  - Prior authorization challenging for privately insured

- Lab payment programs may not be sustainable
  - Safety net clinics rely on lab subsidized testing to get testing done for their patients
  - Limited supply of genetic counselors & limited coverage of genetic counseling may hinder wider testing
  - Varies by population
    - Latinx patients have additional barriers: access for family members, variants specific to this population

Sources: Scheuner et al, Genetics in Medicine, in press; Lin, Trosman et al, under review
Conclusion: Gazing into Crystal Ball - and What CDC Might Consider

• Continued global implementation of NGS tests
  – Need “horizon scanning” aka “feeling the pulse”
  – Need better use of RWD

• Payer coverage and economic value questions will continue
  – Especially as population screening tests emerge
  – Need mechanisms such as EGAPP and ICER to assess evidence – and value

• Payers will increasingly use external companies to manage genetic testing & testing will increasingly be consolidated in large, for-profit labs – with potential implications for cost, access, and disparities
  – Direct-to-consumer health testing will be replaced by labs providing easy access to low-cost clinical-grade testing
  – Need considerations of implications for public health at individual and system level

• *NGS testing is here to stay!*
Thank you!!!