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

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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?

TRUE OR FALSE

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.

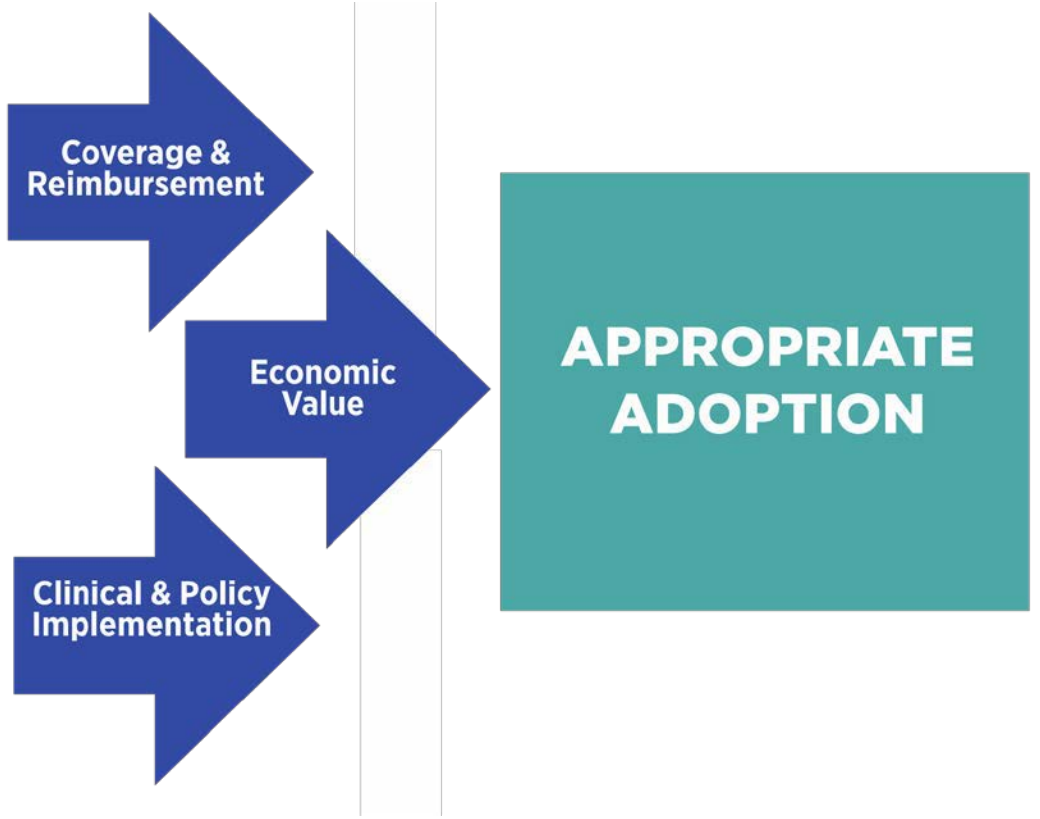
4) *Muin tweets rather than sleeps*

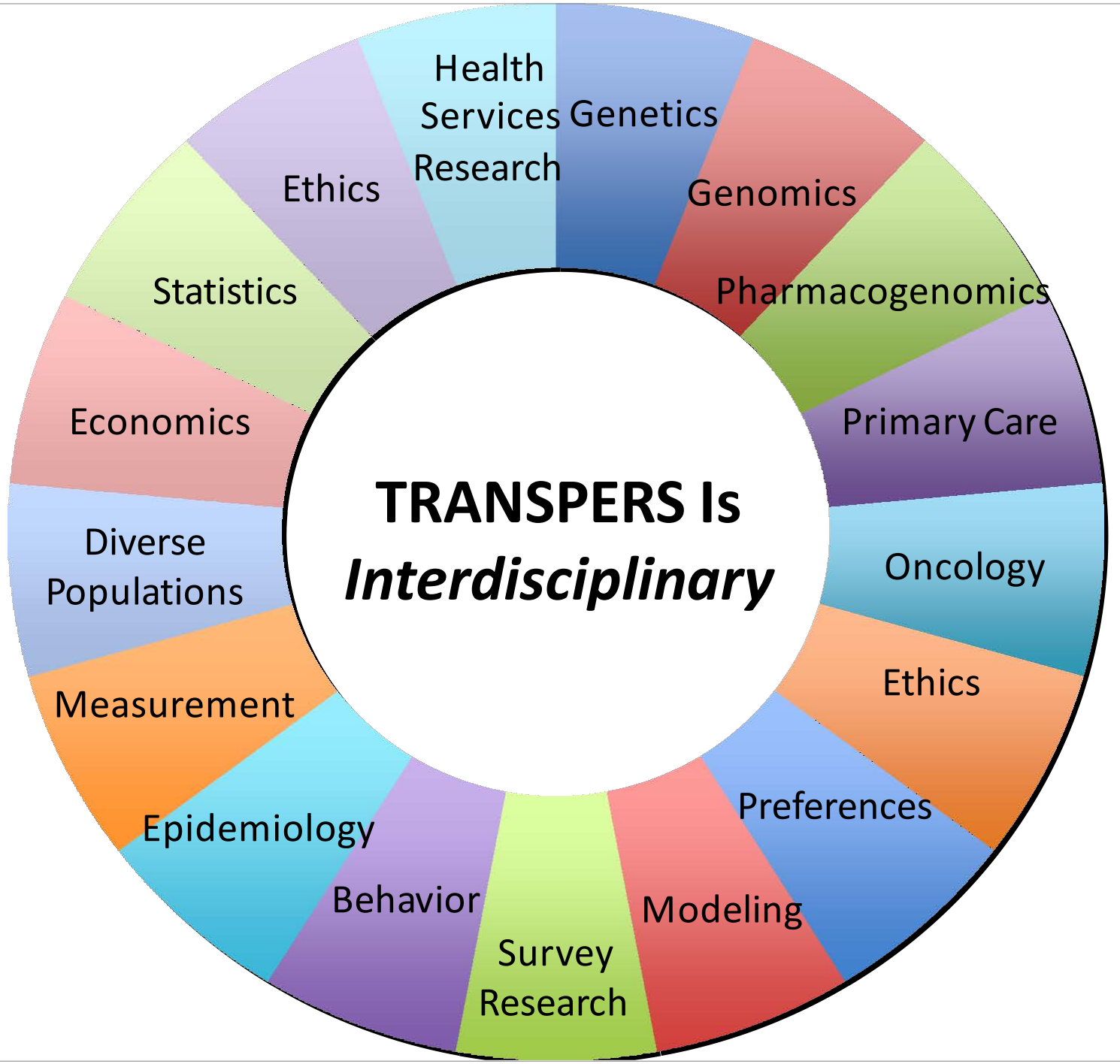
Appears to be true. 3233 followers.

TRANSPERS

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

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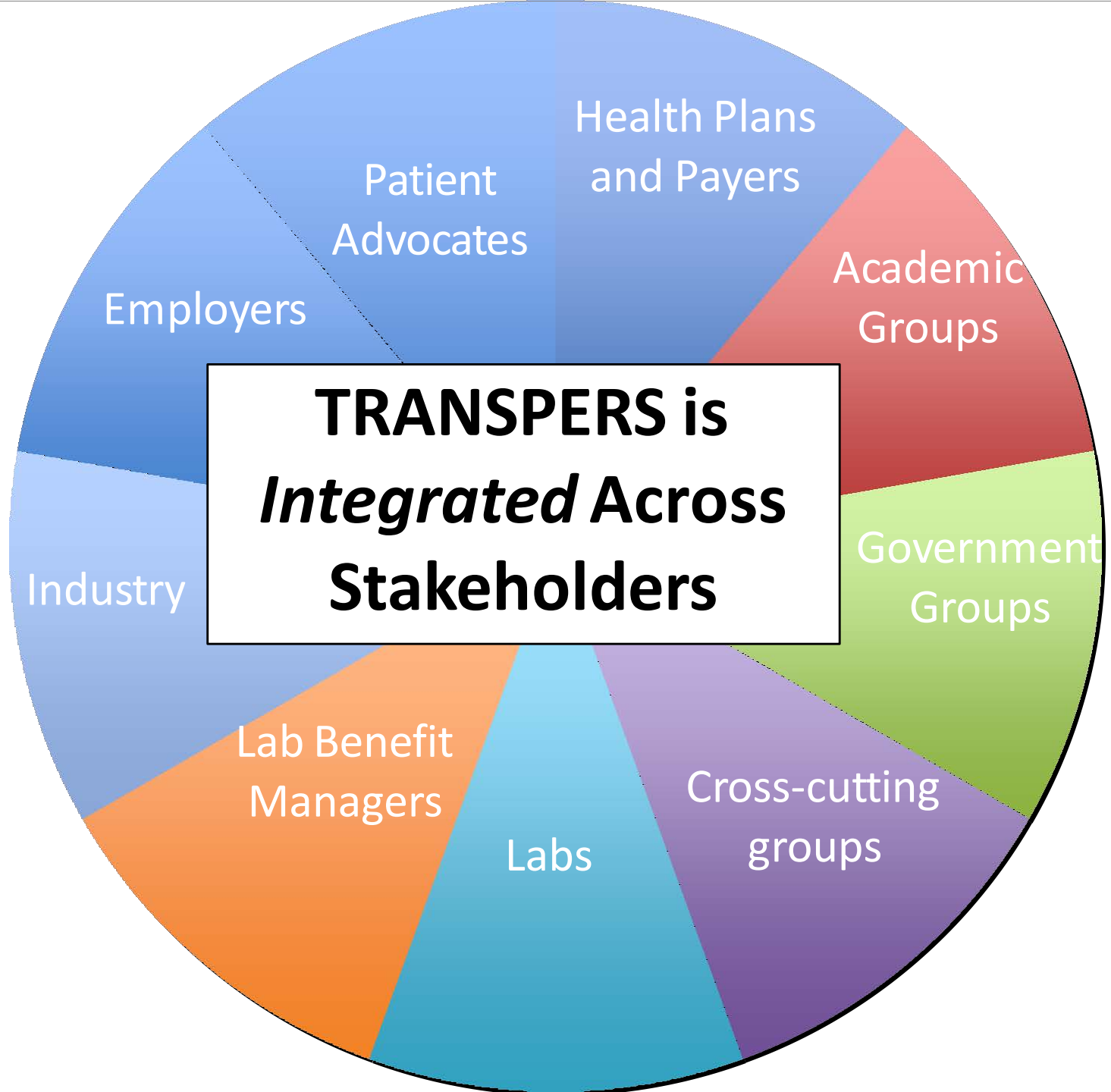

Health Plans and Payers
Academic Groups
Government Groups
Cross-cutting groups
Labs
Lab Benefit Managers
Industry
Employers
Patient Advocates
TRANSPERS is *Integrated* Across Stakeholders


Science
Insurance coverage for genomic tests
April 2018
JAMA
Evolving Payer Coverage Policies on Genomic Sequencing Tests
Beginning of the End or End of the Beginning?
June 2018
JAMA
Expanding Use of Clinical Genome Sequencing and the Need for More Data on Implementation
October 2020
Genetics inMedicine
Private payer coverage policies for exome sequencing (ES) in pediatric patients: trends over time and analysis of evidence cited
Jan 2019
NATURE BIOTECHNOLOGY
July 2017
Payer coverage policies for multigene tests
JAMA
June 2019
Emergence of Hybrid Models of Genetic Testing Beyond Direct-to-Consumer or Traditional Labs
HEALTH AFFAIRS
Genetic Test Availability And Spending: Where Are We Now? Where Are We Going?
May 2018
HEALTH AFFAIRS
The Emerging Use By Commercial Payers Of Third-Party Lab Benefit Managers For Genetic Testing
Oct 2019
JNCCN
Private Payer and Medicare Coverage for Circulating Tumor DNA Testing: A Historical Analysis of Coverage Policies From 2015 to 2019
July 2020
Genetics inMedicine
Perspectives of US private payers on insurance coverage for pediatric and prenatal exome sequencing: Results of a study from the Program in Prenatal and Pediatric Genomic Sequencing (P3EGS)
Sept 2019
Value in Health
Themed Section: Assesing the Value of Next-Generation Sequencing
Assessing the Value of Next-Generation Sequencing Technologies: An Introduction
Sept 2018

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

JAMA

Expanding Use of Clinical Genome Sequencing and the Need for More Data on Implementation

Phillips et al 2020

Center for Translational and Policy Research on Personalized Medicine
University of California, San Francisco

Data Needed on Implementation, Data Gaps, and Possible Data

Implementation Factors	Data Gaps	Possible Data Sources
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

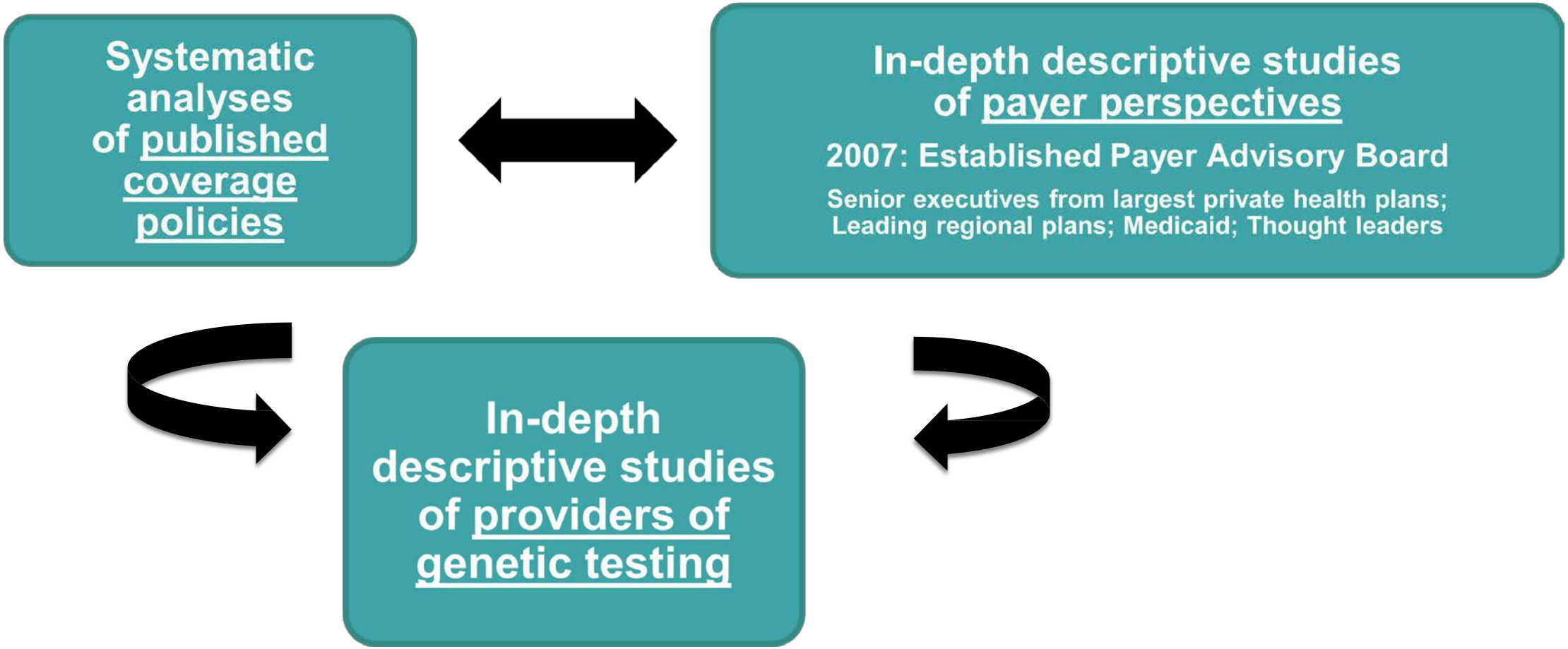
Percentage of Studies by Characteristics (N=39)

RWD Type					Integrated Dataset	Data Challenges Noted*		
Registry	Administrative Commercial	Administrative Public	Clinical	Lab	Used Integrated Dataset for Analyses	Missing Data	Nonspecific Coding	Causal Inference
56%	33%	26%	21%	18%	33%	95%	46%	35%

*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



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

Increase in Coverage for Liquid Biopsy for Cancer Patients by Private Payers and Medicare – but Broader Pan-Cancer Coverage under Medicare

- 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

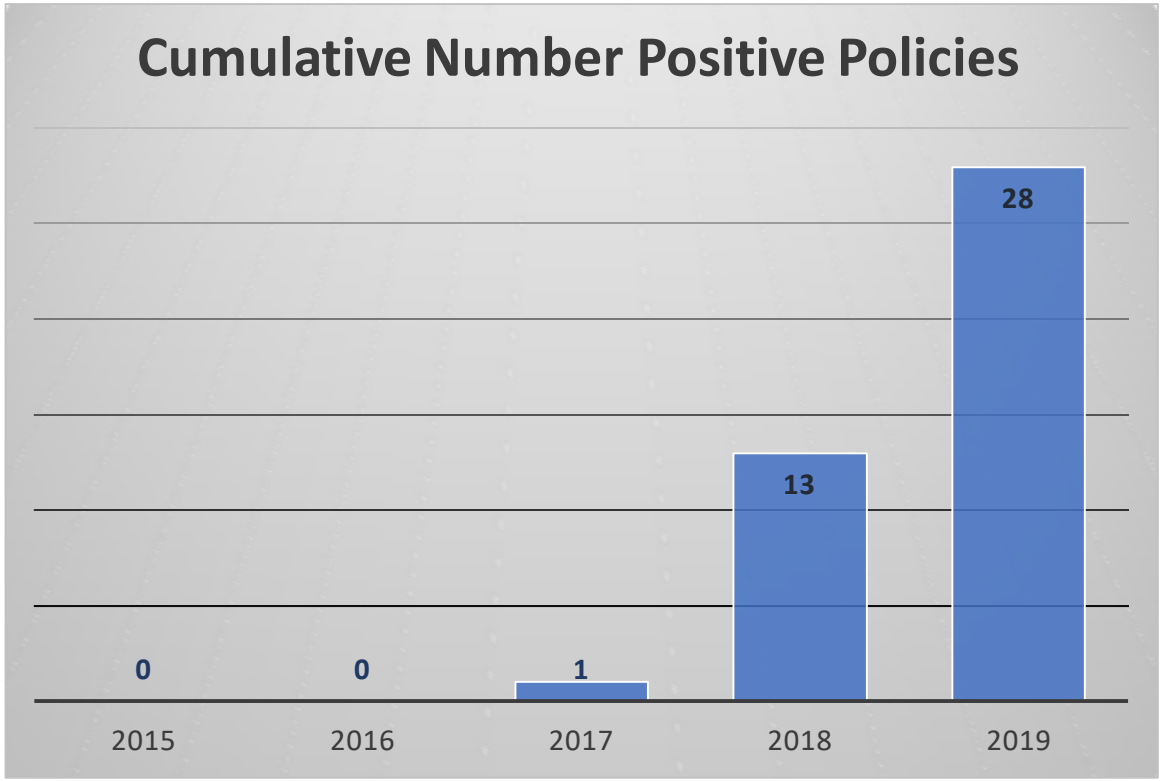
- Why important
  - Less invasive than tumor biopsies and can be used when tissue not available (e.g., lung cancer)
  - Ability to easily monitor response to therapeutic agents
  - May pave the way towards use of tests for early cancer detection

Source: Douglas, Gray, Phillips, JNCCN, 2020

Results:
Rapid Increase in Coverage 2015-2019

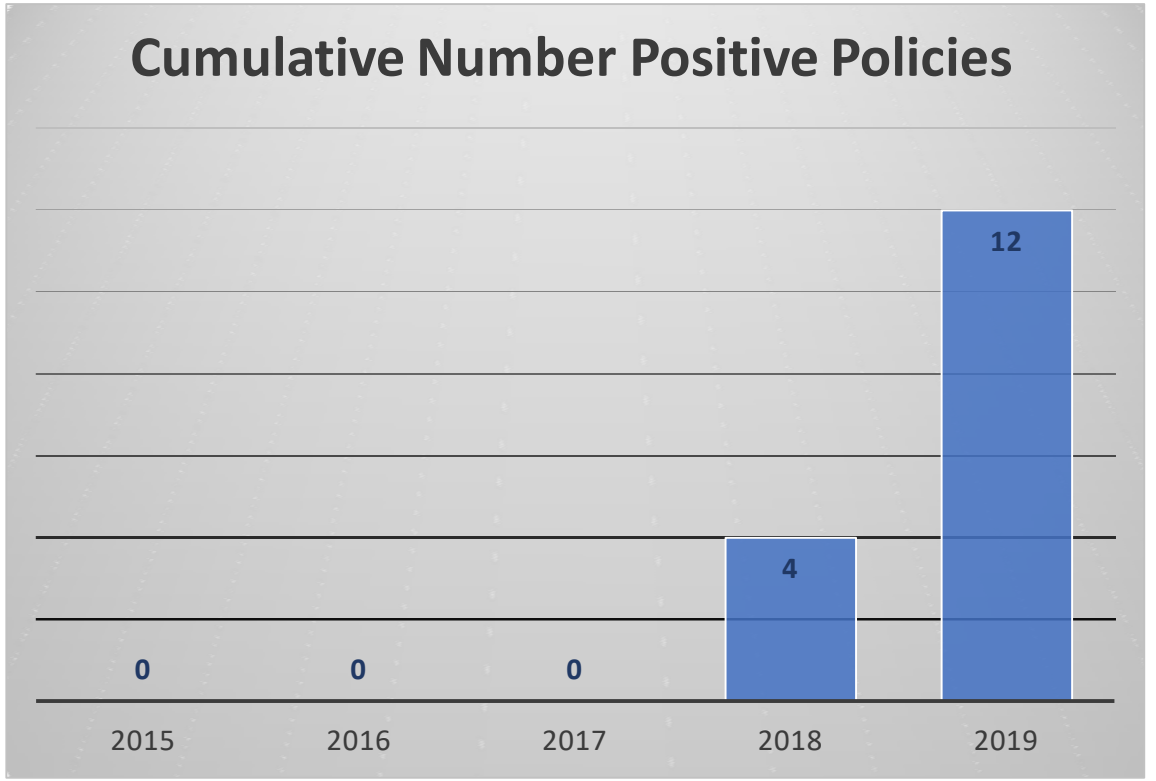
Private Payers:

0% to 38% Coverage

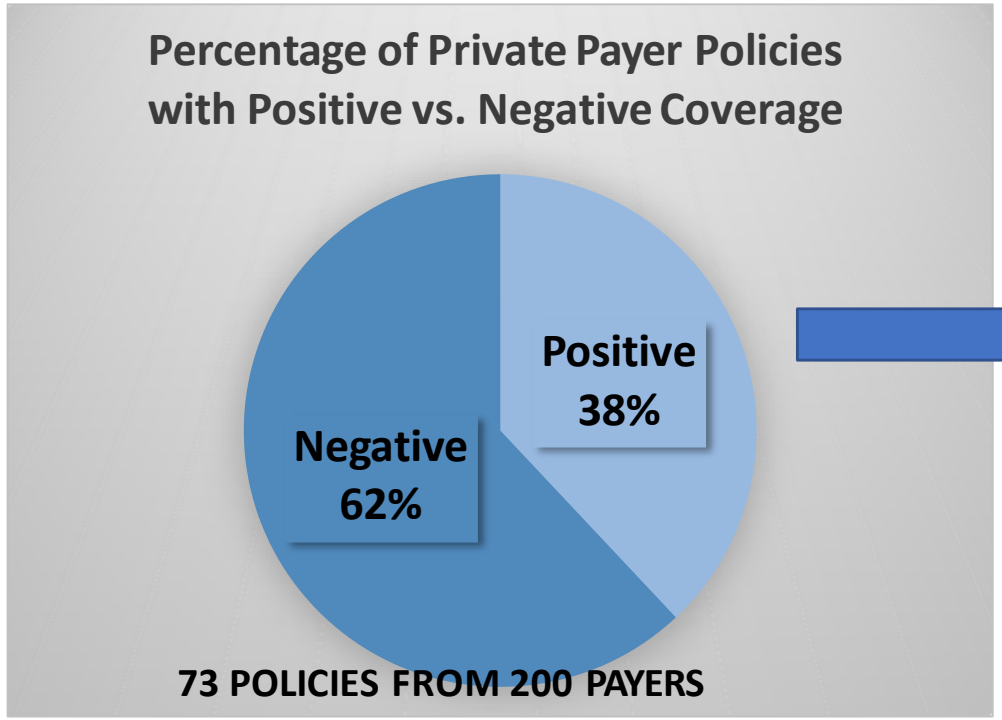


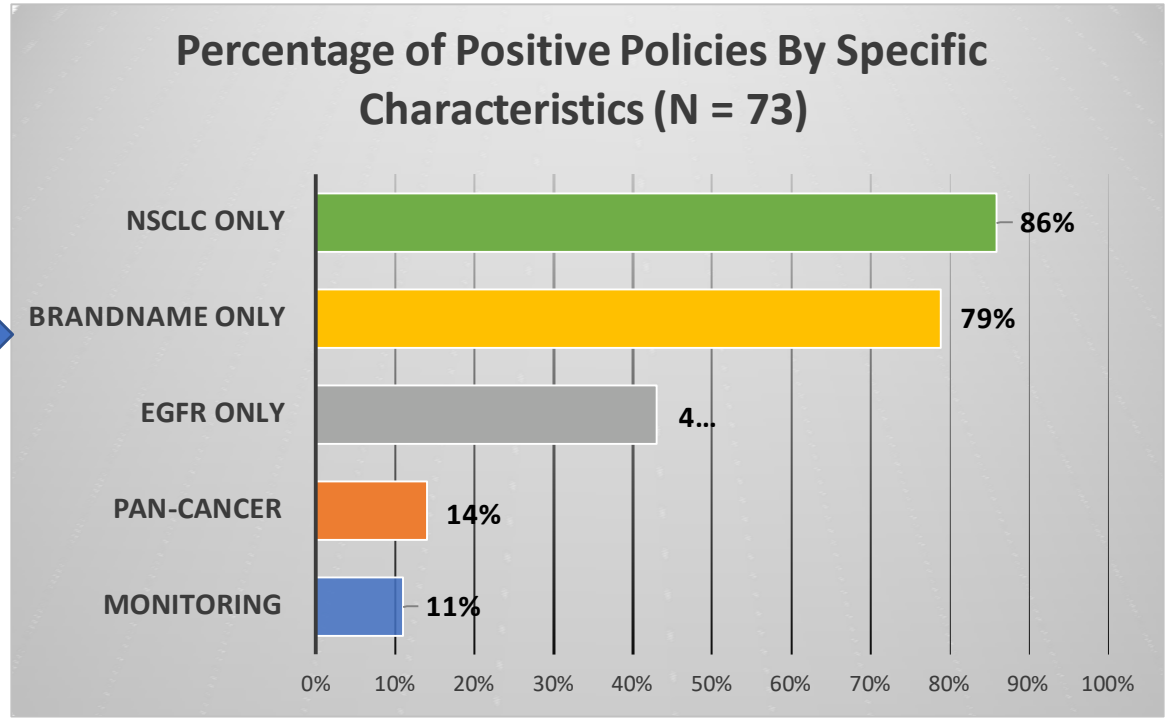
Medicare Local Coverage Determinations:

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





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

UCSF Center for Translational & Policy Research on Personalized Medicine

UCSF TRANSPERS Payer Advisory Board Webinar

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

TRANSPERS 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*)

*Former

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 TRANSPERS

- Kathryn Phillips
- Michael Douglas
- Julia Trosman
- Christine Weldon

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

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

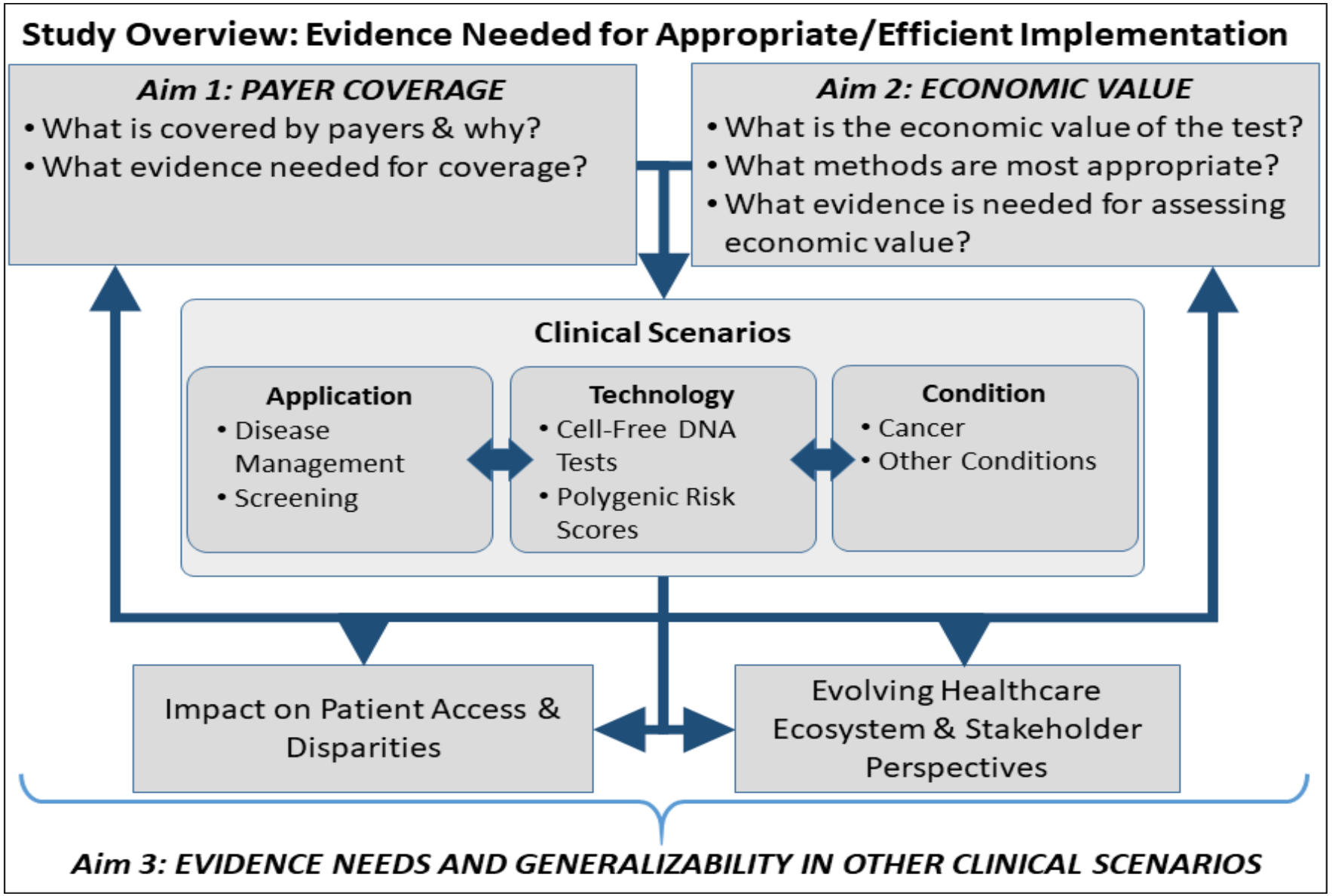
  E.g., ICER’s work on pharmaceuticals incorporates both and is having large influence on industry and payers

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



MIT Technology Review

10 Breakthrough Technologies: Liquid Biopsy

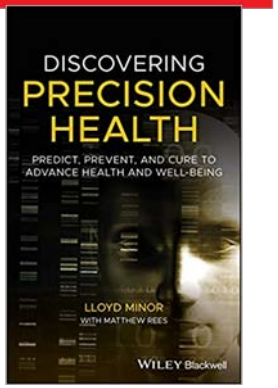
Fast sequencing machines leading to simple blood test for cancer.

- 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"

February 2021

Health Affairs



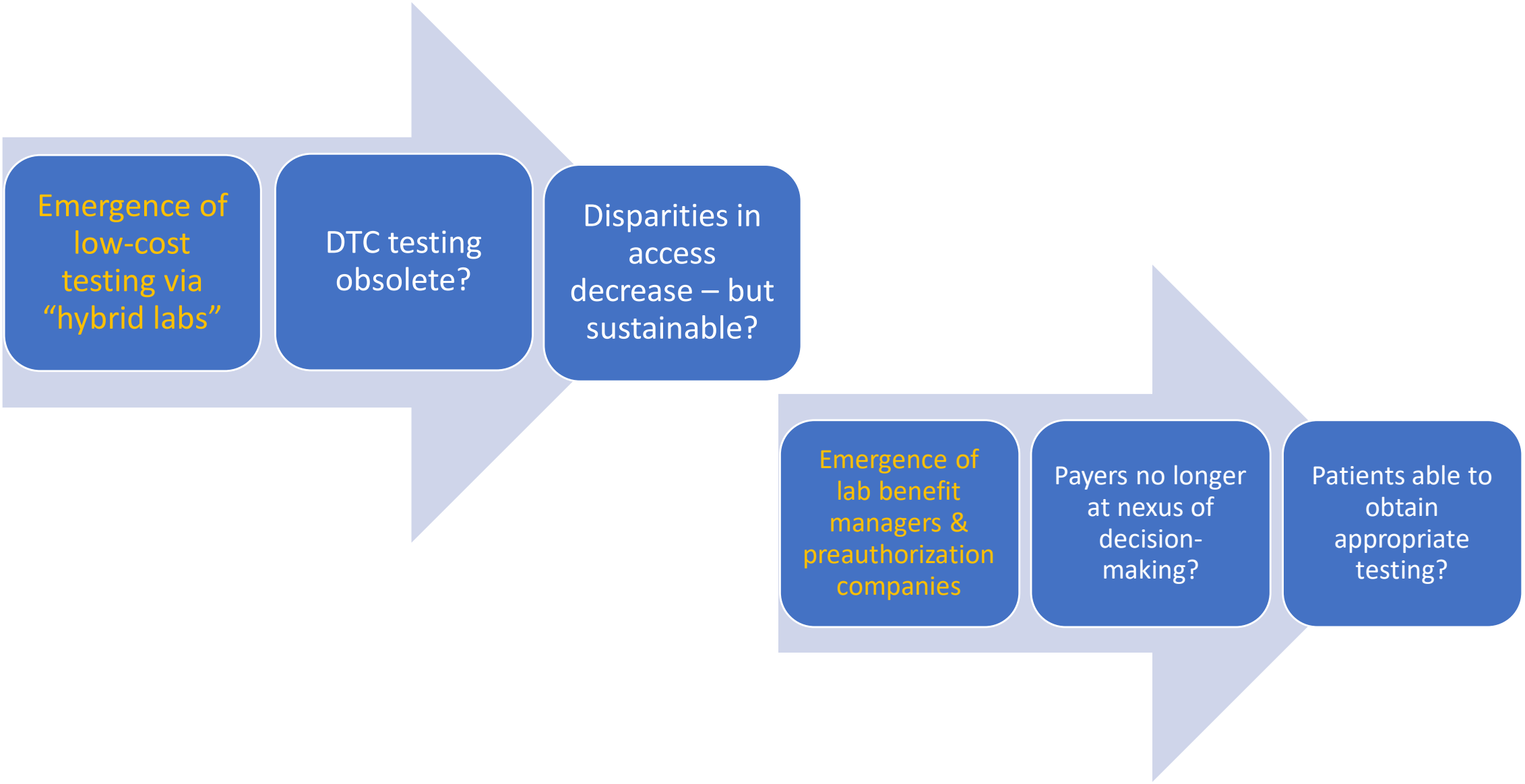
- *Precision Health* leverages omics, immune status, medical imaging, family history, physical condition and standard doctor visits to predict and prevent disease from occurring

Precision Health Smart Toilet Monitors for Signs of Disease

- 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



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

	DTC Model	Hybrid Model	Traditional Model
Primary emphasis	Consumer Access & Information	Consumer Access & Clinical Care	Clinical Care
Central role	Consumer	Consumer & Clinician	Clinician
Testing	Limited	Broad	Broad

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

Source: Phillips et al JAMA 2019

TRANSPERS Studies Finds Emergence of Lab Benefit Managers & Preauthorization Companies

- 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

Company	Date Founded	Ownership	Services Managed	Illustrative Contracted Health Plans
AIM Specialty Health	1989	Anthem (2)	Multiple (3)	- Anthem - Misc. regional plans
Avalon Healthcare Solutions	2013	Private	Lab only	- Multiple Blue Cross Blue Shield plans
Beacon Lab Benefit Solutions	2010	LabCorp	Lab only	- UnitedHealthcare
eviCore	1994 (4)	Cigna (5)	Multiple (3)	- Multiple Blue Cross Blue Shield plans - Highmark - Misc. regional plans
Kentmere Lab Benefit Management Program	2000	Private	Lab only	- Misc. plans (6)

CMT SOLUTIONS
Activating Precision Medicine

STARTING NOV. 1 2017, UHC MEMBERS REQUIRE A PRIOR AUTHORIZATION FOR GENETIC & MOLECULAR LAB TESTING

Source: Phillips & Deverka, Health Affairs 2019

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!*

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