The Role of Cost-Effectiveness in Precision Medicine and Public Health Genomics

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Outline of Presentation

- **Part 1 – Economic evaluation terms and methods**
  - Cost-effectiveness, value, and affordability
  - One size does not fit all
- **Part 2 – Applications in Precision Medicine and Public Health Genomics**
  - Newborn screening for severe combined immunodeficiency (SCID)
  - Ivacaftor – genotype targeted therapy for cystic fibrosis
  - Testing patients with colorectal cancer for Lynch syndrome
  - Genomic sequencing and reporting of secondary results

How Do We Show Value?

- **What is value in health?**
  - Achieving better health in ways that are affordable and acceptable
    - Value is in the eye of the stakeholder
    - Subjective and context-specific
- **How to show value?**
  - Identify your stakeholder audience(s)
  - Assess which costs and outcomes matter to stakeholders
  - Calculate costs and outcomes (benefits) for each type of stakeholder
- **Economic evaluation methods vary**
  - Choose analysis type(s) to meet stakeholder needs

Stakeholder Perspectives

- **Stakeholders**
  - Health care payers
  - Health care providers
  - Public health programs
  - Patients and families (last, but not least!)
- **Cost varies by analytic perspective**
  - Societal – all costs to all payers
  - Health care sector – medical costs for all payers
  - Payer or provider
    - A cost to a payer is revenue to a provider
    - For state agencies, budget impact is crucial
    - Health plans care about their per member per month outlay

What's a Cost?

- **Economic cost – resources used up that cannot be used elsewhere (opportunity cost)**
- **Financial cost – outlays by payers (payments)**
  - Charges or list prices are *not* costs
- **Costs to whom?**
  - Health care costs (economic cost)
    - Costs to specific types of providers or payers (financial costs)
  - Costs outside of the health care system
    - Patients and families
  - Financial costs to public sector (health and non-health) – budgetary impact

Price vs. Cost – Pharmaceuticals

- **Drug prices may bear little relation to costs**
  - Example: Price of Lipitor fell from $3.29 to 11 cents per unit after the patent expired (NASEM 2017)
  - Sudden price increases of >500 percent observed for 48 generic drugs between 2010 and 2015
- **Should cost-effectiveness analyses (CEAs) use prices?**
  - Payer perspective CEAs should use net payments (Hay et al. 2010)
    - Subtract discounts and rebates from gross payments (28 percent of payments on branded drugs rebated by manufacturers – NASEM)
  - Societal perspective CEAs should use societal cost (Hay et al. 2010)
    - Expert panel recommended using range of 20-60 percent of price of branded drugs as estimate of cost

National Academies of Sciences, Engineering, and Medicine. 2017. *Making medicines affordable: A national imperative*. Washington, DC: The National Academies Press. doi: https://doi.org/10.17226/24946

Hay JW, Smeeding J, Carroll NV, et al. Good research practices for measuring drug costs in cost effectiveness analyses: issues and recommendations: the ISPOR Drug Cost Task Force Report part I. *Value in Health*. 2010;13(1):3 7.

Health Outcomes and Beyond Health

- **Health gains**
  - How to measure and value health?
    - Survival
    - Quality of life and functioning
    - Quality-adjusted life-years (QALYs) combine both dimensions
      - Assign utility scores from 0 to 1
        - 0 = death
        - 1 = perfect health
      - Estimated improvement with intervention
- **Beyond health outcomes and QALYs**
  - Personal values – autonomy, knowledge, and fairness
  - Personal utility

What Do Payers and Providers Value?

- **Health for patients (providers) or plan members (payers)**
- **Market share and consumer satisfaction**
  - Higher cost can lower market share, especially for insurers
- **Net revenue (providers) and net payments (payers)**
- **Access to new technologies (providers)**
- **Minimum of political fuss**
- **Ease of implementation**
- **Minimized decisional difficulty**

Economic Evaluation Methods

- **Cost-consequences analysis**
  - Cost per diagnosis – no information on health outcomes
- **Cost-effectiveness analysis (CEA)**
  - Which approach costs less per health outcome gained?
  - CEAs that use quality-adjusted life years (QALYs) often called cost-utility analysis (CUA)
- **Cost-benefit analysis (CBA)**
  - Is the monetary value of benefits to society greater than total cost?
- **Budget Impact Analysis (BIA)**
  - Will financial benefits exceed outlays in a given timeframe for a private payer, public program, or state government overall?

Cost-Effectiveness Analysis (CEA)

- **For each pair of options (e.g., screening vs. no screening, or two different screening algorithms)**
  - Assess total outcomes and costs
  - Treatment costs can go up or down following intervention
  - For pairs of options that cost more and are more effective, calculate incremental cost-effectiveness ratio (ICER)

$$Cost\ effectiveness\ ratio = \frac{intervention\ costs\ - costs\ averted}{change\ in\ health\ outcome}$$

  - ICER is a function of the comparator – One can only assess cost-effectiveness relative to an alternative strategy
    - Not an innate characteristic of an intervention

When Is an Intervention Cost-Effective? – 1

- **Low cost to implement does not mean cost-effective**
  - Effectiveness first, then cost-effectiveness (Grosse 2014)
  - Low cost per case detected is not meaningful unless detection improves outcomes that matter
- **If an intervention is not effective—i.e., demonstrated to improve health outcomes—it cannot be cost-effective**
  - Epidemiology matters – rigorous study designs required to demonstrate improved health (Grosse & Khoury 2016)
  - Multiple sources of bias in observational data
- **Public health screening is warranted based on evidence of meaningful health gains**

Grosse SD. Economic analyses of genetic tests in personalized medicine: clinical utility first, then cost utility. *Genetics in Medicine*. 2014 Mar;16(3):225 227.

Grosse SD, Khoury MJ. Epidemiology matters: peering inside the "black box in economic evaluations of genetic testing. *Genetics in Medicine*. 2016;18(10):963 965.

When Is an Intervention Cost-Effective? – 2

- **Will an intervention that improves health pay for itself, i.e., reduce total costs?**
  - A few interventions or preventive services are cost-saving, i.e., less total spending with intervention than without
  - Most cost-effective services result in higher net costs

Benjamin Franklin famously said that an ounce of prevention is worth a pound of cure, but he didn't say that it is necessarily less expensive. A recent review from the Partnership for Prevention concluded that most recommended clinical preventive services are cost-effective but not cost-saving.[1] A cost-saving intervention results in both better health outcomes and less total spending by payers, including medical care and other direct costs of care, as well as costs associated with the intervention.

- **Cost-effectiveness is the value of services that cost more than they save**

Grosse SD. Does newborn screening save money? The difference between cost effective and cost saving interventions. *Journal of Pediatrics*. 2005; 146(2):168 170.

When Is an Intervention Cost-Effective? – 3

- **Cost effectiveness depends on how much decision makers are willing to pay for health gains**
  - Interventions that cost less than a benchmark value, such as $50,000 per QALY, often regarded as cost-effective
    - Arbitrary; use of a range may be preferable (Grosse 2008)
    - US government does not endorse cost-effectiveness decision rules
  - Institute for Clinical and Economic Review (ICER)
    - Non-governmental US organization has proposed a range of $50,000--$150,000 per QALY to define value (Neumann & Cohen)
    - Potentially greater willingness to pay for orphan drugs
  - CEA findings can be considered by stakeholders, along with equity and affordability considerations

Grosse SD. Assessing cost effectiveness in health care: The history of the $50,000 per QALY threshold. *Expert Review of Pharmacoeconomics and Outcomes Research*. 2008; 8(2):165 178.

Neumann PJ, Cohen JT. ICER's revised value assessment framework for 2017 2019: a critique. *Pharmacoeconomics*. 2017; 35:977 980.

Neumann PJ, Cohen JT. America s "NICE"? *Health Affairs Blog*, March 12, 2018

Why Care About Cost-Effectiveness?

- **Manufacturers and advocates**
  - Marketing and support for access to new technologies
- **Payers**
  - Informed coverage decisions and controlling costs
- **Policy makers**
  - Choosing among alternatives
  - Trade offs among multiple criteria
    - Population health, budget constraints, perceived fairness, and response to advocacy
  - Maximizing vs. satisficing
- **Researchers**
  - Professional advancement

Budget Impact and Return on Investment (ROI)

- **Calculation of net financial cost**
  - Cost outlay and avoided financial costs to same budget holder
  - Short time horizons
    - May be 1-3 years, e.g., some state Medicaid programs
    - Typically 2-5 years
    - Large employers may have 10 year time horizon – low attrition
    - Medicare and state governments may have 10 year time horizon
  - Outcome measures include
    - ROI ratio – X dollars saved for each 1 dollar spent
    - Payback period – how long it takes for intervention to break even
- **Unlike most cost-effectiveness & cost-benefit analyses**
  - Long time horizon and all costs, regardless of who pays & benefits
  - Prevention can be cost-effective but have unfavorable ROI

Beyond Cost-Effectiveness: Clinical and Personal Utility of Diagnostic Testing

- **Clinical utility has two meanings (Grosse & Khoury 2006)**
  - Improvement in health outcomes – required for cost-effectiveness
    - QALYs recommended, not required in CEAs (Carias et al. 2018)
  - Clinical actionability – provider can use diagnostic information to offer new options for clinical management
- **Personal utility of diagnosis (NASEM 2018)**
  - Value that people place on information per se
  - Ability to try new treatments
  - Prognosis even if condition is not currently treatable
  - Implications for relatives

Grosse SD, Wordsworth S, Payne K. Economic methods for valuing the outcomes of genetic testing: Beyond cost effectiveness analysis. *Genetics in Medicine*. 2008; 10(9):648 655.

Grosse SD, Khoury MJ. What is the clinical utility of genetic testing? *Genetics in Medicine*. 2006; 8(7):448 450.

Carias CMD, Chesson H, Grosse SD, et al. Recommendations of the Second Panel a reference for cost effectiveness, not a rule book. *American Journal of Preventive Medicine*. 2018;54(4):600 602.

NASEM. Financial Considerations for Implementing Genomics Based Screening Programs. In: *Implementing and Evaluating Genomic Screening Programs in Health Care Systems: Proceedings of a Workshop*. National Academies Press, 2018.

Part II:
Precision Medicine and Public Health Genomics

- **Precision medicine**
  - Tailoring of therapies to disease subgroups, often defined by genotype
    - Rare, inherited diseases such as cystic fibrosis
    - Molecular subtypes of common diseases such as cancers
    - Tailored drug prescribing – pharmacogenomics
- **Public health genomics**
  - Population-level testing to identify people with at-risk genotypes who can benefit from tailored therapies
    - Initial tests may be biochemical, followed by molecular assay
  - From population screening to diagnostic testing
    - Gene sequencing blurs the boundaries of screening and diagnosis
    - Risk of disease is a continuum, not binary

Examples of Applications for Value Assessment

- **Newborn screening for rare disease – severe combined immunodeficiency (SCID)**
- **Precision medicine – ivacaftor for patients with cystic fibrosis eligible based on genotype**
- **Population genomic applications**
  - Testing for prevalent, highly penetrant genomic variants with actionable interventions
  - Example: Lynch syndrome
    - Tumor testing in patients with colorectal or endometrial cancer
  - Reporting of secondary findings from gene sequencing
    - Opportunistic (clinical) or population-based sequencing
    - Which findings to report?
      - Actionable, untreatable, or variants of unknown significance

Public Health Newborn Screening

- **Screening newborns for congenital disorders to enable presymptomatic diagnosis and treatment**
  - Two types of public health newborn screening (NBS)
    - Point-of-care testing
      - Hearing loss and critical congenital heart disease
    - Laboratory analysis of dried blood collected on filter paper cards
      - More than 30 primary target conditions
      - Phenylketonuria (PKU) in 1963 was first NBS disorder
  - All states and most high-income countries require newborn screening be offered or done
    - 4 million US infants each year undergo testing for inherited and other conditions
    - Most first-tier screening tests are biochemical

Grosse SD, Riehle Colarusso T, Gaffney M, et al. CDC Grand Rounds: newborn screening for hearing loss and critical congenital heart disease. *MMWR Morb Mortal Wkly Rep*. 2017;66(33):888 890.

US Newborn Screening Policy Process

- **State governments decide which disorders to screen**
- **US Department of Health and Human Services (HHS) has a Recommended Uniform Screening Panel (RUSP)**
  - Current RUSP has 34 primary screening targets
  - Advisory Committee on Heritable Disorders in Newborns and Children (Committee) provides recommendations to the HHS Secretary
    - Conditions are nominated for consideration
    - If the Committee decides sufficient evidence is available, a systematic evidence-based review is completed and presented to the Committee
    - The Committee discusses and deliberates on the evidence presented and votes to recommend or not recommend adding the nominated condition to the RUSP
    - The Secretary of HHS makes the final decision on whether to add, or not add a recommended condition to the RUSP

For more information about the RUSP and the nomination process, please visit the Committee's website at www.hrsa.gov/advisory committees/heritable disorders

Severe Combined Immunodeficiency (SCID) aka "Bubble Boy Disease"

- **Group of primary immunodeficiency conditions with extremely low or absent T cells**
  - Genetically heterogeneous
  - Prevalence about 1 in 58,000 US newborns
  - Typical SCID is fatal without treatment in first 2 years of life due to recurrent infections
    - Hematopoietic cell transplant (HCT) is now standard therapy
    - With pre-symptomatic treatment, survival is high (>90 percent)
    - 10-20 percent of infants, who have adenosine deaminase deficient ADA-SCID, can be treated with PEG-ADA enzyme replacement therapy (ERT), gene therapy, or transplant
  - "Leaky" SCID in absence of NBS diagnosed much later; also not usually fatal in first years of life

Kwan A, Puck JM. History and current status of newborn screening for severe combined immunodeficiency. *Seminars in Perinatology*. 2015;39(3):194 205.

Newborn Screening for SCID

- **Screening uses a PCR-based T-cell receptor excision circle (TREC) assay**
  - TREC assay was first molecular first-tier newborn screening test
  - Screening labs needed to add new technology (equipment, staff, and training) to test for SCID
    - Supported by federal agency grants and technical assistance
- **SCID was added to the RUSP in May 2010**
  - Recommended by ACHDNC following evidence review and results from pilot screening projects in two states (Lipstein et al. 2010)
    - Evidence of effectiveness based on clinical studies of late- and early-identified infants with SCID (due mostly to family history)
  - Currently almost all states screen for SCID (NewSTEPS 2018)

Lipstein EA, Vorono S, Browning MF, Green NS, Kemper AR, Knapp AA, Prosser LA, Perrin JM. Systematic evidence review of newborn screening and treatment of severe combined immunodeficiency. *Pediatrics*. 2010; 125(5):e1226 35

https://www.newsteps.org/resources/newborn screening status all disorders

THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGINAL ARTICLES

Cost-Effectiveness/Cost-Benefit Analysis of Newborn Screening for Severe Combined Immune Deficiency in Washington State

Yao Ding, PhD[1], John D. Thompson, PhD[2], Lisa Kobrynski, MD[3], Jelili Ojodu, MPH[1], Guisou Zarbalian, MPH[1], and Scott D. Grosse, PhD[4]

- **Washington Department of Health, CDC, APHL, and Emory University collaborated on study**
- **Washington has 86,600 annual births, with 2 screens per infant**
- **Cost of TREC assays (TREC amplification and a control gene, *beta-actin*) calculated by WDOH @$8.08 per infant**
  - Includes labor, equipment amortization, and reagents
- **NBS short-term follow-up costs $50 per positive screen**
  - No additional clinical cost because no additional visits needed
- **2.9/10000 infants referred for confirmatory flow cytometry testing @ $250**
- **Incremental cost of screening & diagnosis = $8.16 per infant or $741, 376**

Ding Y, Thompson JD, Kobrynski L, Ojodu J, Zarbalian G, Grosse SD. A cost effectiveness/cost benefit analysis of newborn screening for severe combined immune deficiency in Washington State. *Journal of Pediatrics*. 2016 May;172:127 135.

Is Newborn Screening for SCID Cost-Effective?

- **SCID screening saves lives and money (partially)**
  - Survival projected to be 88 percent in early-identified infants vs. 54 percent in late-identified infants
    - ~20 percent of infants with SCID detected early based on family history in unscreened cohort
  - Reduced treatment cost offset 43 percent of screening costs
    - HCT if done early is less expensive – $100,000 vs. $450,000 per infant
    - Net cost of screening: $424,470 ($741,376 – $316,905)
- **ICER = $35,311 per life-year saved**
  - $424,470 divided by 12.02 discounted life years
  - Sensitivity analyses assessed influence of parameter uncertainty
    - ICER <$100,000 per life-year under all plausible assumptions

Ding Y, Thompson JD, Kobrynski L, Ojodu J, Zarbalian G, Grosse SD. A cost effectiveness/cost benefit analysis of newborn screening for severe combined immune deficiency in Washington State. *Journal of Pediatrics*. 2016 May;172:127 135.

Newborn Screening Detects Multiple Disorders

- **Disorders that may be picked up by TREC assay**
  - Typical SCID and "Leaky" SCID, including Omenn syndrome
  - Non-SCID T-cell lymphopenia (TCL)
    - Congenital (genetic) syndromes
      - DiGeorge syndrome or chromosome 22q11 deletion (minority)
    - Other medical conditions – congenital heart disease, preterm birth
    - Idiopathic TCL
  - Pooled data from 11 programs (Kwan et al. 2014)
    - 52 SCID (42 typical SCID)
    - 411 non-SCID TCL
      - 136 congenital syndromes
      - 117 other medical conditions

Kwan A, Abraham RS ,Currier R, et al .Newborn screening for severe combined immunodeficiency in11screening programs in the United States. *JAMA*. 2014;312(7): 729 738.

Limitations of SCID Cost-Effectiveness Analyses

- **CEA studies have not included long-term costs of treating survivors who would otherwise have died**
  - CEA guidelines call for inclusion of future costs
- **No data on impact of SCID on quality of life of children and family members (spill-over effects)**
- **No modeling of costs and outcomes of other diagnoses following positive TREC screens**
- **Uncertainty in treatment cost estimates**
- **Costs of screening may vary based on program choices**
  - Number of specimens tested
  - Choice of assay and implementation

Neumann P, Sanders GD, Russell LB, Siegel JE, Ganiats TG. 2017. *Cost effectiveness in health and medicine: 2nd Edition*. New York: Oxford University Press.

Does Cost-Effectiveness Matter for US Newborn Screening Policy Decisions?

- **Cost-effectiveness not part of decision matrix for recommending additions to RUSP (Kemper et al. 2014; Prosser et al. 2012), but cost to states is now addressed**
- **Affordability (budget impact) may be a concern to state governments**
  - Implementation costs for new technologies can be a barrier
  - Increase in per-infant NBS fee charged to birthing centers depends on cost of screening test
  - Potential indirect effect of a high cost-effectiveness ratio on policy-maker concerns about budget impact

Kemper AR, Green NS, Calonge N, et al. Decision making process for conditions nominated to the Recommended Uniform Screening Panel: statement of the US Department of Health and Human Services Secretary's Advisory Committee on Heritable Disorders in Newborns and Children. *Genetics in Medicine*. 2014;16(2):183 187.

Prosser LA, Grosse SD, Kemper AR, et al. Decision analysis, economic evaluation, and newborn screening: challenges and opportunities. *Genetics in Medicine*. 2012;14(8):703 712.

Precision Medicine Example: Ivacaftor Treatment for Cystic Fibrosis

- **Ivacaftor (Kalydeco®) approved by FDA in Jan 2012**
  - Targets molecular defect associated with *CFTR* gating mutations
  - Originally targeted to patients with the G551D mutation (~4% of US patients with CF)
  - Trial evidence demonstrated marked (~10%) improvement in lung function (FEV_1)
  - FDA approval subsequently expanded to include additional gating mutations as well as R117H mutation
  - Combination of ivacaftor and lumacaftor (Orkambi®) approved by FDA in 2015 for patients with two copies of the common delta-F508 mutation (not addressed in this presentation)

Murphy MP, Caraher E. Current and emerging therapies for the treatment of cystic fibrosis or mitigation of its symptoms. *Drugs in R&D*. 2016;16(1):1 7.

Effectiveness of Ivacaftor

- **Within-individual comparison of patients who took ivacaftor in real-world administrative claims database***
  - Comparison of inpatient admissions during 12 months prior to and 12 months following first filled prescription, 2012 to 2017
  - Self-selection not a problem because vast majority of eligible patients initiated therapy soon after it became available
- **Results**
  - 79% fewer admissions with principal diagnosis of CF (primarily pulmonary exacerbations) year-to-year
  - Effectiveness comparable after FDA added other gating mutations to label in February 2014
  - Cost offset to payers of roughly $10,000 per patient

*MarketScan® Research Databases, Truven Health (an IBM Watson Company), Treatment Pathways™ analytic interface

Cost and Cost-Effectiveness of Ivacaftor

- **Per-patient US price of ivacaftor ~$310,000 per year**
  - Median payment for ivacaftor during 2016 for 89 privately insured patients with ≥10 fills was $307,543* (pre-rebates)
  - Median payment for ivacaftor during 2016 for 12 publicly insured (Medicaid & CHIP) patients with ≥10 fills was $284,608*
- **Cost-effectiveness ratio estimates**
  - UK report (Whiting et al. 2014): £334,000 to £1.27 million per QALY
  - US CEA study (Dilokthornsakul et al. 2016): $3.4 million per QALY
  - New draft report (ICER, March 15, 2018): $1.0 million per QALY

Whiting P, et al. Ivacaftor for the treatment of patients with cystic fibrosis and the G551D mutation: a systematic review and cost effectiveness analysis. *Health Technol Assess* 2014;18(18).

Dilokthornsakul P, et al. Forecasting US ivacaftor outcomes and cost in cystic fibrosis patients with the G551D mutation. *Eur Respir J*. 2016;47:1697 705.

Institute for Clinical and Economic Review. Modulator Treatments for Cystic Fibrosis: Effectiveness and Value: Draft Evidence Report, March 15, 2018

*MarketScan® Research Databases, Truven Health (an IBM Watson Company), Treatment Pathways™ analytic interface

Does High Cost-Effectiveness Ratio for Ivacaftor Matter to US Stakeholders?

- **Small numbers of patients – modest budget impact**
- **Most employer plans cover ivacaftor with low copays**
  - In 2016, median out-of-pocket payment $617.50 ($45 to $12,000)*
  - Uptake among patients with CF in employer-sponsored plans increased from 2.5% in 2012 to 5.8% in 2016*
- **Medicaid & Children's Health Insurance Program (CHIP)**
  - Uptake among patients with CF was 1.6% in 2012 and 2.1% in 2016 in MarketScan Medicaid sample*
- **Institute for Clinical and Economic Review**
  - Draft Evidence Report (2018)
  - Proposed 50% price reduction to reach $500,000 per QALY value

Institute for Clinical and Economic Review. Modulator Treatments for Cystic Fibrosis: Effectiveness and Value: Draft Evidence Report, March 15, 2018

*MarketScan® Research Databases, Truven Health (an IBM Watson Company), Treatment Pathways™ analytic interface

CDC's Tier 1 Genomic Testing Applications

- **Satisfy at least one of 3 criteria:**
  - Clinical practice guideline with systematic evidence review
  - CMS covers testing (Medicare national coverage determination)
  - FDA label requires use of genomic test to inform choice or dose of a drug or there is a FDA approved companion diagnostic device
- **CDC Genomic Applications toolkit focuses on:**
  - Hereditary Breast and Ovarian Cancer syndrome – increased risk for breast and ovarian cancers due to *BRCA1* or *BRCA2* mutations
  - Lynch syndrome (LS) – increased risk for colorectal, endometrial, and ovarian cancers from mutations in four DNA mismatch-repair (MMR) genes (*MSH2*, *MLH1*, *MSH6*, *PMS2*), as well as *EPCAM*
  - Familial hypercholesterolemia (FH) – increased risk for heart disease or stroke due to mutations leading to very high cholesterol levels from an early age

Lynch Syndrome

- **Autosomal dominant disorder accounting for 2-3 percent of colorectal and endometrial cancers**
  - 50% of first-degree relatives (FDRs) share same mutation
- **Cumulative risk of colorectal cancer (CRC) 40 percent**
  - Varies by gene
- **Identifying carriers allows for cancer prevention**
  - Surveillance (colonoscopy each year) starting at age 25
    - Reduces CRC incidence by almost 60 percent
    - Reduces mortality even more due to more favorable staging of cancer
  - Prophylactic hysterectomy to prevent endometrial cancer
  - Aspirin 600 mg/d reduces risk of CRC by 59 percent

Boland PM, Yurgelun MB, Boland CR. Recent progress in Lynch syndrome and other familial colorectal cancer syndromes. *CA: A Cancer Journal for Clinicians*. 2018 Feb 27, ePub ahead of print.

Testing Methods to Identify Lynch Syndrome

- **Cascade testing – identify proband, then test relatives**
  - Preliminary testing of tumor tissue in newly diagnosed cancers
    - Microsatellite instability (MSI) testing for presence of MMR mutations
      - Clinical sensitivity
        - *MLH1* or *MSH2* – 85 percent
        - *MSH6* – 55 to 77 percent
      - Clinical specificity – 90 percent
    - Immunohistochemistry (IHC) testing of MMR gene proteins
      - Clinical sensitivity – 83 percent
      - Clinical specificity – 90 percent
  - Second-tier gene sequencing following positive preliminary tests
  - Or direct sequencing of cancer patients
- **Gene sequencing of people without cancer**
  - Population-based or based on risk prediction scores

Alternative Approaches to Test for LS in Patients with Newly Diagnosed CRC

- **Universal testing vs. reflex testing of adults with newly diagnosed cancers**
  - Maximizes sensitivity but with lower yield
- **Selective testing**
  - Based on age cutoffs of 50, 60, or 70 years
  - Family history and tumor pathology
- **Selective testing can detect most cases of LS**
  - Research study: Moreira et al. (2012)
    - Jerusalem (≤70 years) – 85 percent of LS cases
    - Revised Bethesda Guidelines (RBG) criteria – 88 percent of LS cases
  - Uncertain if family history data is reliably collected in routine care

Moreira L, Balaguer F, Lindor N et al. Identification of Lynch syndrome among patients with colorectal cancer. *JAMA*. 2012, 308, 1555 1565.

Lynch Syndrome Testing Recommendations

- **EGAPP (Evaluation of Genetic Applications in Practice and Prevention) – 2009**
  - Universal tumor testing in all newly diagnosed CRC patients
    - Skeptical of reliably identifying family history in clinical care
  - Biochemical testing using IHC, with or without testing for *BRAF* mutation, or MSI
- **Multi-Society Task Force on Colorectal Cancer – 2014**
  - Testing of newly diagnosed CRC tumors, using either:
    - Universal testing, or
    - Testing all patients <age 70 and older patients with family history concerning for LS

EGAPP Working Group. Genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. *Genetics in Medicine*. 2009;11(1):35 41.

Giardiello FM, Allen JI, Axilbund JE, et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi society Task Force on colorectal cancer. *American Journal of Gastroenterology*. 2014;109(8):1159 1179.

Cost-Effectiveness of Lynch Syndrome Testing

- **Multiple CEAs of testing for LS in CRC**
  - Comparisons of strategies to identify probands
    - Tumor testing in all patient vs. no patients
    - Tumor testing in patients under specified age (60, 70) vs. no patients
    - Tumor testing in all patients vs. under an age cutoff (50, 60 years)
    - Tumor testing in all patients vs. selective testing based on age, family history, and tumor pathology
    - Direct gene sequencing vs. tumor testing followed by gene sequencing
- **Three reviews of published CEAs**

Grosse SD. When is genomic testing cost effective? Testing for Lynch syndrome in patients with newly diagnosed colorectal cancer and their relatives. *Healthcare*. 2015;3:860 878.

Assasi N, Blackhouse G, Campbell K, Weeks L, Levine M. *Mismatch repair deficiency testing for patients with colorectal cancer: a clinical and cost effectiveness evaluation*. Ottawa, Ontario CADTH;2015.

Di Marco M, D'Andrea E, Panic N, et al. Which Lynch syndrome screening programs could be implemented in the "real world"? A systematic review of economic evaluations. *Genetics in Medicine*. 2018 Jan 4; Epub ahead of print.

Cost-Effectiveness Findings: Universal vs. No Testing

Study	Country	Strategy	Comparator	ICER (Nearest 100 US Dollars)	
				Per LY saved	Per QALY gained
Universal *vs.* No Testing					
Mvundura *et al.* [32] & Grosse *et al.* [27]	USA			$ 25,100—original $ 34,900—updated	$ 29,600—original
Ladabaum *et al.* [31] & Wang *et al.* [33]	USA			$ 38,700	$ 63,900
Barzi *et al.* [30]	USA			$ 46,900^	

- Universal tumor testing cost-effective if alternative is no testing at all
  - Most cost-effective strategy: IHC testing, followed by BRAF testing, then sequencing
- However, CEAs should include all feasible alternatives
  - Age-targeted testing
  - Selective testing based on family history, tumor pathology, and age

Grosse SD. When is genomic testing cost effective? Testing for Lynch syndrome in patients with newly diagnosed colorectal cancer and their relatives. *Healthcare*. 2015;3:860 878.

ICERs for Universal vs. Selective Testing

(from Grosse 2015)

Age-Targeted Testing Strategies					
Mvundura *et al.* [32]	USA	<50 years	No testing	$ 8,700	
		No limit	<50 years	$ 41,200	
Ladabaum *et al.* [31]	USA	≤50 years	No testing	$ 29,900	
		≤60 years	≤50 years	$ 36,200	
		≤70 years	≤60 years	$ 47,300	
		No limit	≤70 years	$ 94,900	
Sie *et al.* [34]	Netherlands	≤70 years	≤50 years	Dominant (cost-saving)	
Snowsill *et al.* [29,35]	UK	<50 years	No testing		$ 8,400
		<60 years	No testing		$ 11,800
		<70 years	No testing		$ 16,600
Age and Family History-Based Testing					
Ladabaum *et al.* [31]	USA	MMRpro	No testing	$ 32,700	
		Universal	MMRpro	$ 125,200	
Severin *et al.* [14]	Germany	RBG	No testing	$ 106,100	
		Universal	RBG	$ 347,700	
Barzi *et al.* [30]	USA	MMRpro	No testing	$ 35,100 ^	
		Universal	MMRPro	$ 144,100 ^	

Is Testing for Lynch Syndrome Cost-Effective? It Depends!

- **Cost-effectiveness is a function of the comparator**
  - Consistent findings
    - Universal testing is cost-effective relative to no testing
    - Direct gene sequencing is not cost-effective, but that could change
    - Universal testing may not be cost-effective relative to selective testing based on family history, age, and tumor pathology
  - Unclear findings
    - Is universal testing cost-effective relative to testing patients <age 70?
- **Cost-effectiveness also depends on**
  - Willingness to pay
  - Assumptions about effectiveness and costs

Grosse SD. Is universal tumor testing for Lynch syndrome cost effective? It depends! (letter to the editor). *Genetics in Medicine*. Forthcoming.

Other Influences on Cost-Effectiveness of Testing for Lynch Syndrome in CRC

- **Key parameters in cost-effectiveness models**
  - Cost and accuracy of testing and counseling
  - Number of carriers detected per proband
    - Numbers of first-degree relatives (FDRs)
    - Number of FDRs who are offered mutation testing
    - Uptake of mutation testing among FDRs
  - Penetrance (added risk or incidence of cancer)
  - Adherence to colonoscopy every 1 to 2 years
  - Effectiveness in reducing incidence and mortality
    - Impacts on health-related quality of life uncertain, often left out of CEA models

Grosse SD. When is genomic testing cost effective? Testing for Lynch syndrome in patients with newly diagnosed colorectal cancer and their relatives. *Healthcare*. 2015;3:860 878.

Is Lynch Syndrome Cascade Testing Cost-Effective from Stakeholder Perspective?

- **Budget impact less favorable to specific payers since benefits accrue to other payers who cover FDRs**
  - Integrated health systems and self-insured employers with lower turnover in membership more likely to incur future benefits
- **Payer perspective less influential than provider choices**
  - Payers usually reimburse for "medically necessary" services
  - What factors affect decisions by providers and health systems to implement universal testing for Lynch syndrome? (Schneider 2016)
    - Desire to meet evolving standard of care
    - Concerns about budgets and logistical challenges are barriers
    - Some leaders believe that testing will eventually pay for itself in reduced cost of care – very unlikely to happen

Schneider JL, Davis J, Kauffman TL, et al. Stakeholder perspectives on implementing a universal Lynch syndrome screening program: a qualitative study of early barriers and facilitators. *Genetics in Medicine*. 2016;18(2):152 161.

Challenges in Evaluating Cascade Testing for Lynch Syndrome

- **Lack of population-level documentation**
  - How many CRC and endometrial cancer patients are tested for Lynch syndrome each year?
  - What is the frequency of universal vs. selective testing?
  - Which testing strategies are most commonly used?
  - How many first degree relatives are contacted and tested?
  - How many carriers adhere to colonoscopy every 1 to 2 years?
- **Cost-effectiveness is dependent on identifying carriers and providing effective care to minimize cancer risks**

Beyond Lynch Syndrome: Multi-Gene Panels to Test Patients with Colorectal Cancer

- **Gallego et al. (2015) modeled use of next-generation sequencing (NGS) panels of multiple genes in place of standard-of-care testing for Lynch syndrome**
  - For patients suspected of having a hereditary CRC syndrome
    - Sequencing MMR genes alone not cost-effective
    - Sequencing both MMR genes and other genes associated with highly penetrant cancer syndromes was cost-effective
  - For all CRC patients
    - Cost to test for multiple genes using NGS > $70,000 per QALY
    - Possibly cost-effective, depends on willingness to pay

Gallego CJ, Shirts BH, Bennette CS, et al. Next Generation Sequencing Panels for the Diagnosis of Colorectal Cancer and Polyposis Syndromes: A Cost Effectiveness Analysis. *Journal of Clinical Oncology*. 2015;33(18):2084 2091.

Reporting Findings from Clinical Sequencing

- **Clinical use of exome and genome sequencing to establish diagnoses: reporting other gene variants**
  - American College of Medical Genetics and Genomics (ACMG)
    - In 2013, ACMG listed 53 genes for which "incidental" findings could be reported to patients (Green et al. 2013)
    - 2016 ACMG Secondary Findings list expanded to 59 genes for which findings could be medically actionable (Kalia et al. 2016)
  - Framework for assessing clinical actionability (Hunter et al. 2016)
    - Penetrance – probability of serious clinical outcome >5 percent
    - Effectiveness – highly effective intervention with low risk

Green RC, Berg JS, Grody WW, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genetics in Medicine*. 2013;15:565 574.

Kalia SS, Adelman K, Bale SJ, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. *Genetics in Medicine*. 2017;19:249 255.

Hunter JE, Irving SA, Biesecker LG, et al. A standardized, evidence based protocol to assess clinical actionability of genetic disorders associated with genomic variation. *Genetics in Medicine*. 2016;18:1258 1268.

Opinions Differ on Which Variants Are Actionable

- **University of North Carolina NCGENES project (Adams et al. 2016)**
  - Defined pathogenic variants of 17 genes associated with 11 Mendelian disorders
    - Includes *BRCA*1/2 and MMR genes associated with Lynch Syndrome, and *LDLR* associated with familial hypercholesterolemia
    - Long QT syndrome (*KCNQ1*, *KCNH2*, *SCN5A*), Marfan syndrome (*FBN1*)
    - Hereditary hemochromatosis (*HFE*) – specifically homozygous C282Y
      - Not included in ACMG panel (Grosse et al. 2017)
      - Moderate penetrance – 8-10% risk of severe liver disease
      - Highly effective, low-risk intervention – monitoring of serum ferritin and phlebotomy

Adams MC, Evans JP, Henderson GE, Berg JS. The promise and peril of genomic screening in the general population. *Genetics in Medicine*. 2016;18:593 599.

Cost-Effectiveness of Reporting Actionable Findings

- **Decision analysis of reporting findings of ACMG 2013 list of 56 genes for 24 conditions (Bennette et al. 2015)**
  - Next-generation genomic sequencing (NGS) scenarios
    - Secondary findings from clinical NGS
    - Healthy patients – genomic screening
- **Results**
  - Results vary by type of findings reported – excluding sunk cost of sequencing
    - Reporting *BRCA*1/2 mutations is cost-saving
    - Reporting MMR mutations highly cost-effective ($3500 per QALY)
  - Overall NGS process may be cost-effective for some patient groups
  - Not cost-effective as genomic screening unless NGS costs <$500

Bennette CS, Gallego CJ, Burke W, Jarvik GP, Veenstra DL. The cost effectiveness of returning incidental findings from next generation genomic sequencing. *Genetics in Medicine*. 2015;17(7):587.

When Clinical and Personal Utility Diverge

- **Demand for diagnoses of untreatable conditions**
  - Canadian choice experiment (Regier et al. 2015)
  - Wisconsin observed choices study (Bishop et al. 2017)
  - RTI study: Parents want to know if infant has untreatable condition with high penetrance (≥75 percent), severe outcomes (disability or early death), and early onset (age <5 years) (Lewis et al. 2018)
- **What can stakeholders do?**
  - Be cautious – "Look before you leap" (Grosse et al. 2009)
  - Optional screening programs can respond to consumer demand

Regier DA, Peacock SJ, Pataky R, et al. Societal preferences for the return of incidental findings from clinical genomic sequencing: a discrete choice experiment. *CMAJ* 2015;187:E190 97.

Bishop CL, Strong KA, Dimmock DP. Choices of incidental findings of individuals undergoing genome wide sequencing, a single center s experience. *Clinical Genetics*. 2017;91(1):137 140.

Lewis MA, Stine A, Paquin RS, et al. Parental preferences toward genomic sequencing for non medically actionable conditions in children: a discrete choice experiment. *Genetics in Medicine*. 2018;20(2):181 189.

Grosse SD, McBride CM, Evans JP, Khoury MJ. Personal utility and genomic information: Look before you leap. *Genetics in Medicine*. 2009; 11(8):575 576.

Should Personal Utility Be Included in CEAs?

- **Societal utility includes personal and clinical utility**
  - Stakeholders may have differing perceptions and values
  - CEAs conventionally include utility measures expressed in QALYs – do not include personal utility
    - US Second Panel suggests that societal CEAs quantify both health and non-health effects (Neumann et al. 2017)
  - Patient perspective on risks and benefits is increasingly considered by drug regulators
- **NASEM workshop report on genomic screening**
  - Dean Regier proposed incorporating consumer willingness to pay (personal utility) into CEAs (Chapter 3, NASEM 2018)
  - Doing so can increase probability testing is cost-effective

Neumann P, Sanders GD, Russell LB, Siegel JE, Ganiats TG. 2017. *Cost effectiveness in health and medicine: 2nd Edition*. New York: Oxford University Press.

NASEM. Financial Considerations for Implementing Genomics Based Screening Programs. In: *Implementing and Evaluating Genomic Screening Programs in Health Care Systems: Proceedings of a Workshop*. National Academies Press, 2018.

Conclusions

- **Epidemiology matters**
  - Limited evidence of effectiveness can be weak link in CEAs
- **Comparisons matter**
  - Cost-effectiveness of a screening test or treatment is not an innate characteristic but depends on context
- **Cost-effective does not mean cheaper**
  - Genomic diagnosis and prevention may reduce some medical costs but are unlikely to pay for themselves
  - Cost-effectiveness and budget impact both matter
- **Patient perspective is getting more attention**
  - Personal utility of genomic knowledge and precision medicines important part of value proposition

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