COST AND VALUE OF GENOMIC SEQUENCING PROCEDURES

Aaron Bossler, MD, PhD
Clinical Associate Professor
Department of Pathology, University of Iowa
Director - Molecular Pathology Laboratory
Chair - AMP Economic Affairs Committee

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Outline

- Project rationale
- Overview of the Cost Analysis Component
  - Micro-costing
- Overview of the Economic Value Component
  - Payer-cost impact modeling
- Results and implications

Evolution of Molecular Pathology CPT Codes

2010
- AMA Ad Hoc Molecular Pathology Workgroup develops structure through a few face to face meetings and weekly conference calls

2011
- Coding Change Proposals submitted for the next 12 tri-annual cycles

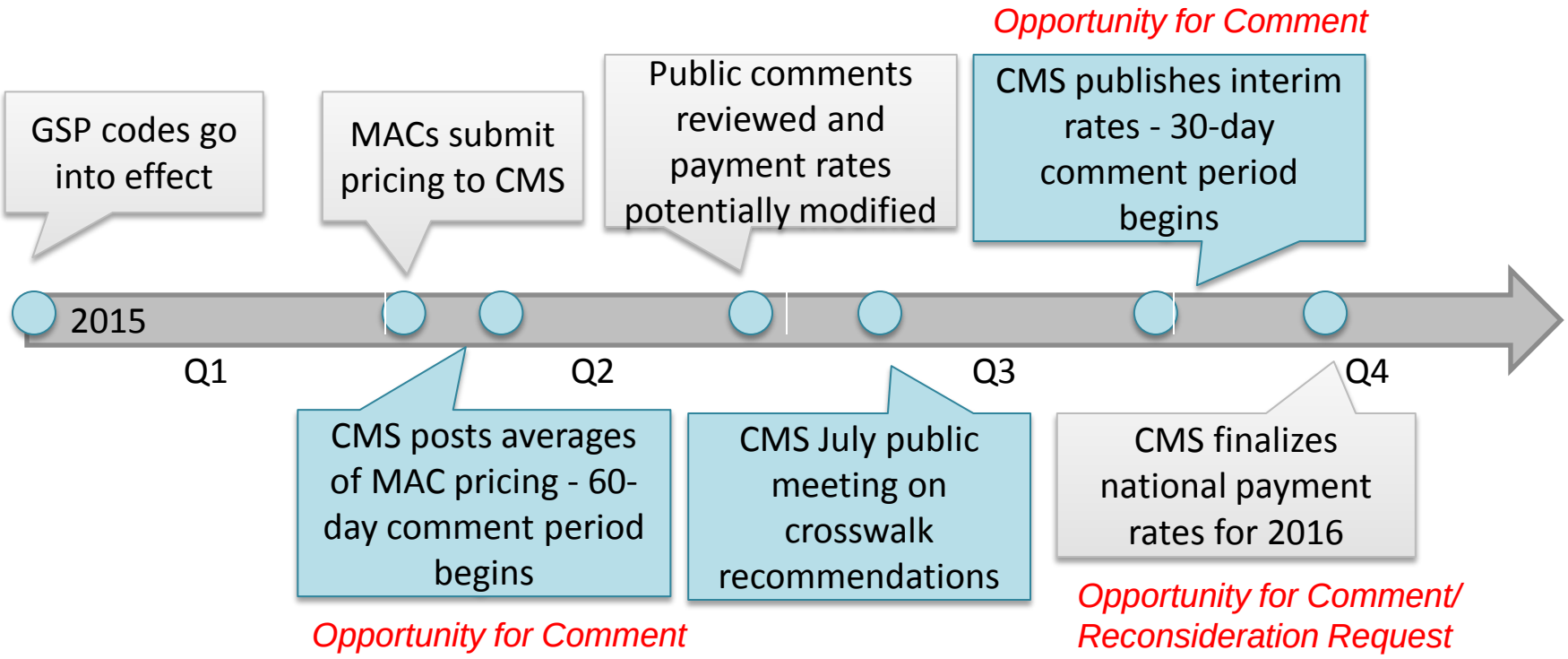
2012
- First Tier 1 and Tier 2 codes published in CPT
- Placement of codes on CLFS in November and initiation of gap filling

2013
- AMP genomic sequencing procedures (GSP) draft proposal to AMA
- 21 AMA workgroup descriptors developed and submitted

2014
- CPT Editorial Panel accepts GSPs for Jan 1, 2015 effective date
- CMS places codes on CLFS and initiate gap filling

2015
- **AMP performs cost and value analyses**

Gap-fill Pricing Requires a Year to Set and Delays Reimbursement



Several consequences...

Consequences of Molecular Pathology CPT Gap Fill

Payment

- CLFS placement/ gap-filling process
- Denials due to absence of pricing
- Undervaluation
- Failure to price all codes

Coverage

- Local Coverage Decisions on DZ specific codes
- LCDs on entire set of codes
- MolDx Program: non-coverage due to Statutory Exclusion
- De facto National Medicare Coverage?
- Medicaid, Private Payers

Coding

- Palmetto MolDx unique identifier
- McKesson Z codes
- AMA Mapping Z to CPT: Codebridge

PAMA Legislation: HR 4302

2014

- New tests for which new payment method applies are those for which a new or revised HCPS code is issued after 4/1/14
- **Payment for new laboratory tests subject to current cross-walking and gap-filling processes thru 2016**

2015

- *By 1/1/15:* MACs required to abide by existing (LCD) process
- *By 6/30/15:* HHS Secretary must issues rules on parameters for data collection
- *By 7/1/15:* Secretary of HHS required to consult with an expert advisory panel

2016

- "Applicable laboratories" must report to CMS certain private market data related to payment rates and test volume

2017

- *Beginning 1/1/17:* Prices based on "weighted median" prices of private market data will become new payment rates

2018-19

- Reductions in payment to laboratories for a given test may not exceed 10%/year

Cost and Value Project Overview

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Genomic Sequencing Procedures CPT Framework

- Categorized GSPs by disease indication
  - Encompassing technical and analytical work
  - Does not include physician professional work
- Targeted multiple gene sequence
  - Aortic dysfunction
  - Hereditary cancer syndromes
  - Nonsyndromic hearing loss
  - X-linked intellectual disability
  - Mitochondrial disorders
  - Targeted somatic tumor mutations
- Fetal aneuploidy
- Exome sequencing
- Genome sequencing

Challenge of Current CPT Paradigm

- NGS technology enables a shift from single analyte to large swaths of DNA with multiple gene panels, exome or genome sequence analysis.
  - The implications are not yet fully understood.
- The code descriptors are “non-specific” on purpose, i.e. they refer to relevant genes
  - Though we know it’s the mutations in the genes that are being identified
  - Payers want to know what “target” was tested for but not just for sake of diagnostic but now also for prognostic or therapeutic significance

Cost and Value Assessment Project

Cost-base of GSP	Value-base of GSP

• Objective: define real world costs in a typical clinical lab
• Includes
  • Technical wet lab
  • Analysis and bioinformatics
  • Assay development
  • Overhead/indirects
	• Objective: Create tools for defining economic value
	• Use payer cost impact modeling for representative procedures.

- Tynan Consulting & Boston Healthcare Associates collected and organized the data
- Industry Support obtained from BioReference Laboratories, Roche, Agilent and BD

Five Representative Procedures Selected

81415	Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis
81430	Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); genomic sequence analysis panel, must include sequencing of at least 60 genes, including CDH23, CLRN1, GJB2, GPR98, MTRNR1, MYO7A, MYO15A, PCDH15, OTOF, SLC26A4, TMC1, TMPRSS3, USH1C, USH1G, USH2A, and WFS1
81470	X-linked intellectual disability (XLID) (eg, syndromic and non-syndromic XLID); genomic sequence analysis panel, must include sequencing of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2
81445	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA and RNA analysis when performed, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed

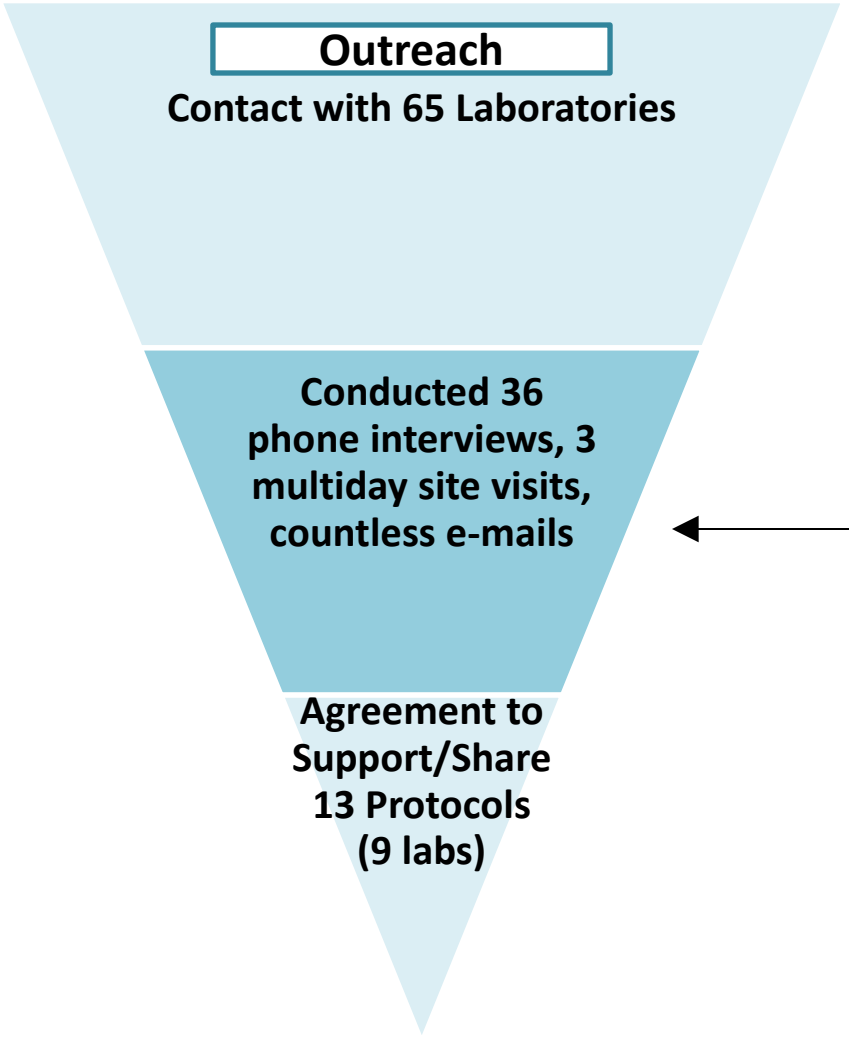
Micro-Costing

Micro-Cost to Capture All Components Driving Assay Cost

Application	Description
Cost of Consumables/Supplies	Pricing for consumables and supplies
Equipment	Use of equipment associated with protocol Usually depreciated or attributed on a per test basis
Bioinformatics/Reporting	Software (commercial or internally developed), equipment, and time used to assess data generated by GSP
Personnel Time	Hands on time by laboratory personnel and those involved in reporting results (analysts, laboratory directors)
Validation, Maintenance, Overhead	Time and cost associated with preparing and keeping the assay ready for clinical use

These procedures require developing costing for development and use of bioinformatic pipeline, curation and reporting of results by higher skilled labor, and data storage

Clinical Laboratory Input



- Objective: identify 3-5 laboratories per assay category
- Result: obtained 13 total protocols
  - Representative of “typical” laboratories
  - Perform at least one run of 5 or more samples per week
  - Clinical testing for at least 6 months

Breadth of Laboratories and Platforms Evaluated

Lab Type	Test Offering	Platform
AMC	81445, Targeted panel, solid organ neoplasm, DNA analysis, 5-50 genes)	Ion Torrent
Commercial	81445, Targeted panel, solid organ neoplasm, DNA analysis, 5-50 genes)	Ion Torrent
AMC	81445, Targeted panel, solid organ neoplasm, DNA analysis, 5-50 genes)	Ion Torrent
AMC	81445, Targeted panel, solid organ neoplasm, DNA analysis, 5-50 genes)	MiSeq
AMC	81445, Targeted panel, solid organ neoplasm, DNA analysis, 5-50 genes)	MiSeq
Commercial	81455, Targeted panel, 51 or greater genes)	MiSeq
AMC	81470, X-linked intellectual disability	HiSeq
AMC	81430 , Hearing loss	HiSeq
Commercial	81430 , Hearing loss	HiSeq
AMC	81430 , Hearing loss	MiSeq
AMC	81415, exome	HiSeq
Commercial	81415, exome	HiSeq
AMC	81415, exome	NextSeq

Detailed Micro-Costing Model

Individual Protocol Steps

Supplies/ Consumables

Reagent/ Equipment List

Personnel Time/Cost

Assay Section		Reagents and Disposables (Consumables)						Equipment					Personnel			
	Steps	Consumables	Consumable Cost	Qty	Unit	Batch Size	Cost per Step	Equipment Used	Equipment Cost	Equipment Time (min)	Quantity	Cost per Step	Personnel Type	Hands On Personnel Time (min)	Personnel Cost Per Min	Cost per Step
DNA Extraction																
	lood or tumor)															
	lity of each DNA sample relative to be made by dilution.															
	idization of strand specific leotide primed extension and															
	nding on platform. Some the Agilent SureSelect, Roche's n and Fluidigm's Access Array.						$ -					$ -				$ -
	e barcodes to samples. Paramagnetic beads are used for cleanup prior to quantification.						$ -					$ -				$ -
Library Quantification & Normalization	Assessment of the quality and quantity of each library. Libraries are normalized by appropriate dilution.						$ -					$ -				$ -
Library Denaturing & Pooling	Libraries are combined into a single pool and denatured.						$ -					$ -				$ -
Sequence Generation	Sequencing performed by Ion Torrent, MiSeq, HiSeq, etc.						$ -					$ -				$ -
Documentation	Recording run metrics						$ -					$ -				$ -
Initial Data Review/Quality Assessment	Review of FAST-Q or BAM file data to ensure correct reads have been made and it is ready for further analysis using pipeline software						$ -					$ -				$ -
Bioinformatics Pipeline Analysis	Analysis of file using bioinformatics software						$ -					$ -				$ -
	Computer support for software						$ -					$ -				$ -
Bioinformatics Output Initial Review	Analysis of output of bioinformatics pipeline using data visualization software						$ -					$ -				$ -
Assay Gap-filling Testing	Sanger Sequencing						$ -					$ -				$ -
Confirmatory Testing	Sanger Sequencing						$ -					$ -				$ -
Report Generation & Sign Out	Comparison of data to reference gene databases						$ -					$ -				$ -
	Generation of draft report						$ -					$ -				$ -
	Review/QC/sign-out of report						$ -					$ -				$ -
Data Storage	Long term/Short-term Data Storage of data on computers, back-up systems						$ -					$ -				$ -
Validation	Time/effort to validate the assay (see software and upkeep tab)						$ -					$ -				$ -
Maintenance	On-going upkeep of analyzer and software systems						$ -					$ -				$ -
		Overal Total														
	Totals Per Section without VMO	$ -					$ -					$ -				$ -
	Total Per Sample without VMO	#DIV/0!					#DIV/0!					#DIV/0!				#DIV/0!

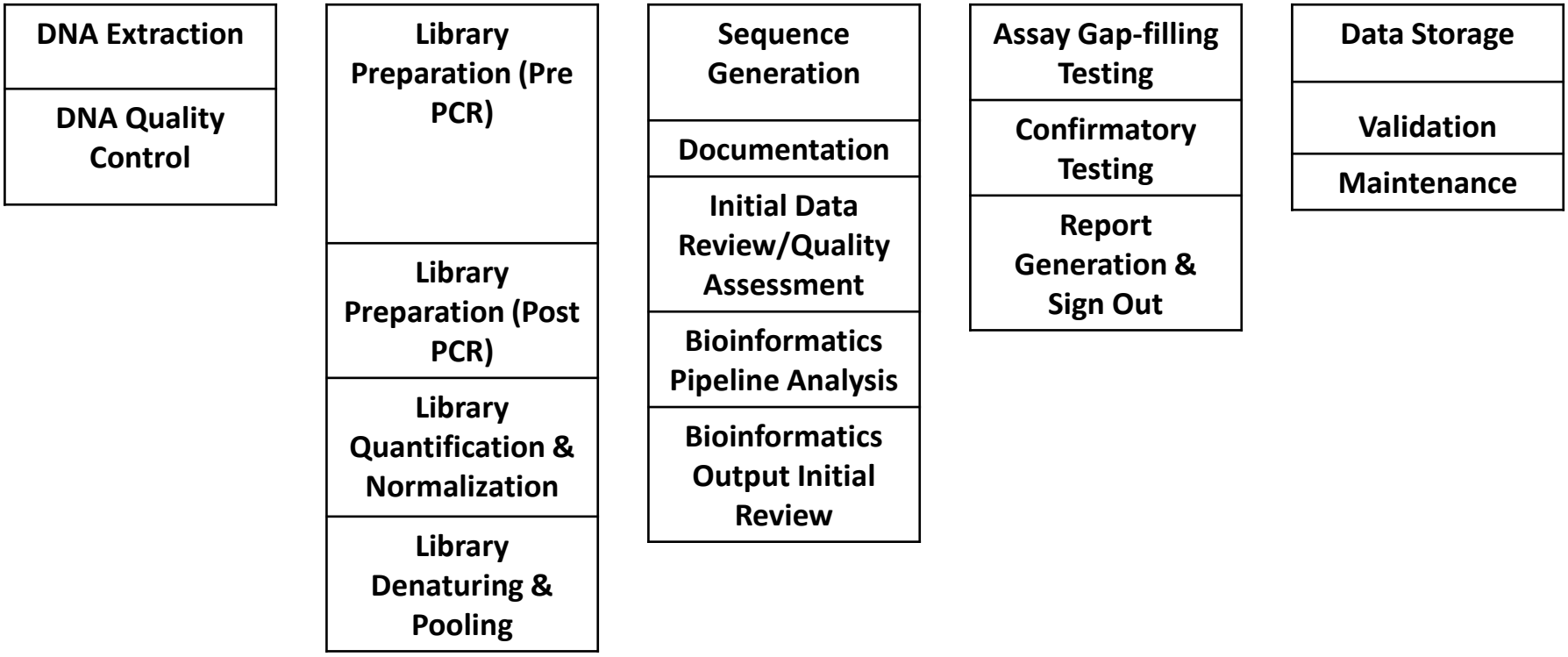
Micro-Cost Worksheets; Columns

Reagents and Disposables (Consumables)					
Consumables	Consumable Cost	Qty	Unit	Batch Size	Cost per Step
					$ -

Equipment				
Equipment Used	Equipment Cost	Equipment Time (min)	Quantity	Cost per Step
				$ -

Personnel			
Personnel Type	Hands On Personnel Time (min)	Personnel Cost Per Min	Cost per Step
			$ -

Micro-Cost Worksheets; Assay Sections



Summary Page; Modifiable by Test Type

Scroll below for By Test Method

By Test Type

	N
Tumor Less than 50 Genes	5

Labor Time	Time	Min	Max
Pre-Analytics/Analytics Labor Time	83.30	41.25	113.22
Post-Analytics Labor Time	64.96	35.00	89.50
Total Labor Time	148.27	76.25	202.72

Costs	Cost		
Pre-Analytics/Analytics Consumables Cost	$ 308.10	$ 267.65	$ 348.80
Pre-Anaytics/Analytics Equipment Cost	$ 17.02	$ 9.48	$ 29.11
Pre-Analytics/Analytics Clinical Labor Cost	$ 31.39	$ 12.45	$ 50.29
Bioinformatics/Data Analysis/Report Creation Cost	$ 127.34	$ 85.50	$ 243.49
Validation, Maintenance, and Overhead Cost	$ 226.24	$ 56.31	$ 395.09
Total Cost of GSP Execution	$ 710.09	$ 431.40	$ 1,066.78

Summary Page; Modifiable by Method

By Method

Module	Module Selection		Cost	N	Min	Max
Sample Type/DNA Extraction	Blood (Automated)	$	9.86	4	$ 6.77	$ 11.56
Library Preparation	Agilent SureSelect	$	352.00	6	$ 173.33	$ 495.28
Sequencing Platform	Illumina HiSeq	$	800.49	5	$ 455.83	$ 1,092.43
Bioinformatics/Data Analysis/Report Creation	Laboratory Director Review Custom	$	131.07	8	$ 61.71	$ 255.75
Validation/Maintenance and Overhead		$	250.30	13	$ 53.56	$ 410.21
Total Cost of GSP Execution		$	1,543.72		$ 751.21	$ 2,265.22

Aggregated Detailed Comparison

Version 1.0

3/3/2015

		Tumor Less than 50 Genes					Tumor Greater than 50 Genes	Targeted Genetics Panel				Whole Exome		
Description		A targeted panel of genes designed to identify actionable mutations which may have treatment implications for oncology patients. May be pan-cancer or focused on particular tumor type.						A targeted panel of genes associated with genetic/hereditary conditions which may explain difficult to diagnose symptoms				A whole exome panel used to assess causes of development delay in children)		
Protocol		1	2	3	4	5	6	7	8	9	10	11	12	13
Offering		< 50 tumor panel	< 50 tumor panel	< 50 tumor panel	< 50 tumor panel	< 50 tumor panel	> 50 tumor panel	X-linked (as part of consolidated genetic panel workflow)	Hearing loss (as part of consolidated genetic panel workflow)	Hearing loss	Hearing loss	Whole Exome	Whole Exome	Whole Exome
Average Batch Size		5	5	6	7	8	6	8	9	8	8	10	8	5
Sample Type/DNA Extraction Method		Tumor (Automated)	Blood (Manual)	Tumor (Manual)	Tumor (Manual)	Tumor (Automated)	Tumor (Manual)	Blood (Manual)	Blood (Automated)	Blood (Automated)	Blood (Manual)	Blood (Automated)	Blood (Manual)	Blood (Manual)
Library Preparation Method		Ion AmpliSeq	Ion Ampliseq	Ion Ampliseq	Trusight Tumor	Trusight Tumor	Custom	Agilent SureSelect	Custom	Agilent SureSelect	Agilent SureSelect	Agilent SureSelect	Agilent SureSelect	Agilent SureSelect
Sequencing Platform		Ion Torrent	Ion Torrent	Ion Torrent	Illumina MiSeq	Illumina MiSeq	Illumina MiSeq	Illumina MiSeq	Illumina HiSeq	Illumina HiSeq	Illumina HiSeq	Illumina HiSeq	Illumina HiSeq	Illumina NextSeq
Bioinformatics/Data Analysis/Report Creation		Laboratory Director Review Custom Pipeline	Laboratory Director Review Custom Pipeline	Laboratory Director Review Custom Pipeline	Laboratory Director Review Custom Pipeline	Laboratory Director Review Commercial Pipeline	Laboratory Director Review Commercial Pipeline	Laboratory Director Review Custom Pipeline	Laboratory Director Review Custom Pipeline	Group Review Custom Pipeline	Laboratory Director Review Custom Pipeline	Laboratory Director Review Custom Pipeline	Group Review Custom Pipeline	Group Review Custom Pipeline
Total Labor Time	DNA Extraction	12	18.8	55	26	11	10	15	0	4	12	0	12	24
	Library Prep	31	26.62	44	34	25	31	93	36	41	20	128	72	149
	Sequencing	13	68	13	34	5	20	4	18	6	3	18	5	6
	Data Analysis	13	22	8	26	38	158	95	25	276	175	45	10	95
	Report Development	45	60	20	30	15	53	45	17	90	120	12	840	204
	Review/Sign-Out	9	8	8	10	15	45	45	3	45	8	4	13	25
Total Pre-Analytics/Analytics Consumables Cost	DNA Extraction	$ 6.28	$ 12.25	$ 10.21	$ 7.92	$ 5.47	$ 10	$ 5.50	$ 5.56	$ 4.76	$ 7.66	$ 3.30	$ 7.66	$ 2.80
	Library Prep	$ 207.68	$ 216.64	$ 181.87	$ 159.14	$ 163.08	$ 477	$ 465.84	$ 195.59	$ 157.92	$ 180.60	$ 420.22	$ 276.25	$ 431.78
	Sequencing	$ 85.30	$ 91.62	$ 75.56	$ 137.24	$ 180.25	$ 279	$ 123.85	$ 364.58	$ 788.18	$ 984.82	$ 314.90	$ 988.70	$ 806.20
Total Pre-Analytics/Analytics Equipment Cost	DNA Extraction	$ 0.15	$ 0.05	$ 0.23	$ 0.00	$ 0.09	$ 4	$ 10.00	$ 3.00	$ 0.96	$ 0.03	$ 3.30	$ 0.03	$ 10.00
	Library Prep	$ 3.12	$ 1.67	$ 10.22	$ 1.34	$ 7.56	$ 13	$ 1.51	$ 1.56	$ 3.26	$ 8.85	$ 1.33	$ 17.10	$ 2.41
	Sequencing	$ 6.21	$ 8.11	$ 6.89	$ 17.99	$ 21.46	$ 109	$ 14.31	$ 112.94	$ 101.84	$ 93.89	$ 135.53	$ 103.73	$ 64.10
Total Pre-Analytics/Analytics Labor Cost	DNA Extraction	$ 3.60	$ 5.64	$ 13.33	$ 13.71	$ 3.38	$ 10	$ 4.50	$ 3.00	$ 1.05	$ 3.53	$ 3.30	$ 3.53	$ 7.20
	Library Prep	$ 9.43	$ 7.99	$ 23.20	$ 18.29	$ 6.94	$ 30	$ 27.94	$ 10.67	$ 12.15	$ 0.12	$ 38.40	$ 21.60	$ 44.70
	Sequencing	$ 3.95	$ 20.34	$ 6.76	$ 18.29	$ 2.14	$ 19	$ 1.13	$ 5.40	$ 1.80	$ 0.75	$ 5.40	$ -	$ 1.80
Total Bioinformatics / Data Analysis /Reporting Cost		$ 85.50	$ 243.49	$ 66.38	$ 110.00	$ 131.30	$ 699	$ 160.12	$ 65.57	$ 670.88	$ 255.75	$ 61.71	$ 1,669.59	$ 659.10
Total Validation Maintenance Overhead Cost		$ 287.34	$ 300.02	$ 194.77	$ 197.66	$ 56.31	$ 298	$ 99.33	$ 279.77	$ 206.67	$ 354.29	$ 410.21	$ 300.00	$ 398.36
Total Assay Cost (Per Sample)		$ 698.57	$ 907.82	$ 589.43	$ 681.58	$ 577.99	$ 1,948	$ 914.03	$ 1,047.64	$ 1,949.47	$ 1,890.27	$ 1,397.60	$ 3,388.18	$ 2,428.45

Cost Differences - Considerations

- Each protocol was unique so costs landed in different spots
- Key cost drivers were:
  - Kit reagents
  - Equipment
  - Reporting
  - Personnel time
- The more DNA assessed the more expensive the assay
- The greater the number of specimens in the run the lesser the overall costs (up to the batch size)
- Significant variation in validation and assay development expenses from first version to later versions
- Group reviews cost significantly more than reviews done mainly by pipeline

Tumor Panel Findings

- Costs were close in range for 81445
  - $578 - $908
    - Variation be platform, investment in lab-developed or commercial bioinformatics and validation expenses
- Assays mostly based on commercial hotspot mutation panels from Ion Torrent or Illumina
  - Methods do not typically include dup/del, CNV or translocation testing
- Paired normal tissue testing for germ-line mutation determination was sometimes performed; we did not include those costs
- Clinical testing in CLIA laboratories is expanding

Hearing Loss Panel Findings

- Costs for 81430 were very narrow in range
  - $1890 - $1949
- Panels had mostly same set of genes
- Largest variance in cost at technical sequencing and bioinformatic analysis components
- Duplication/deletions are typically assessed via another technology (microarray, PCR, FISH) and therefore were not included in micro-costing

Exome Findings

- There was a broader range of cost for 81415
  - $1639 - $3142
- Greater cost variability for technical sequencing and variant evaluation (with same platform and method)
- Clinical testing is a relatively recent offering
- Focus is on the “medical” exome (variations with known significance)

Health Economic Modeling

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Health Economic Modeling

Objective

- Estimate and compare the cost-utility of genomic sequencing procedures with that of standard testing and medical intervention

Design Principles

1) Payer cost Impact Modeling:
    - Avoidance of costs (eg procedures, visits, imaging, side effects, adverse events)
2) Transparency
3) Flexibility to change inputs

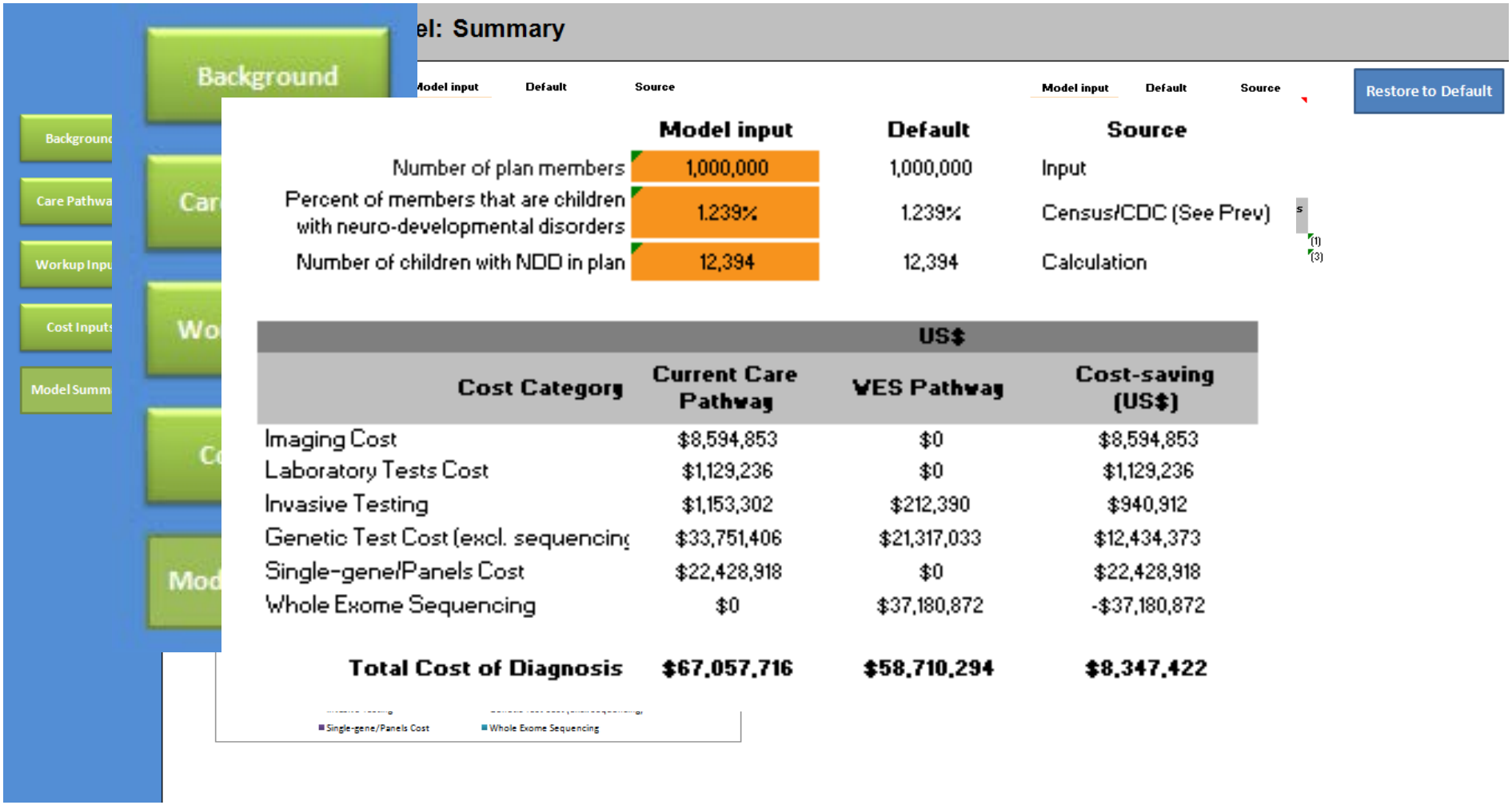
HE Modeling Steps

1) Define current diagnostic and treatment pathways
    - Literature review
    - KOL consultation
2) Develop and program US Payer-oriented Cost Impact Model

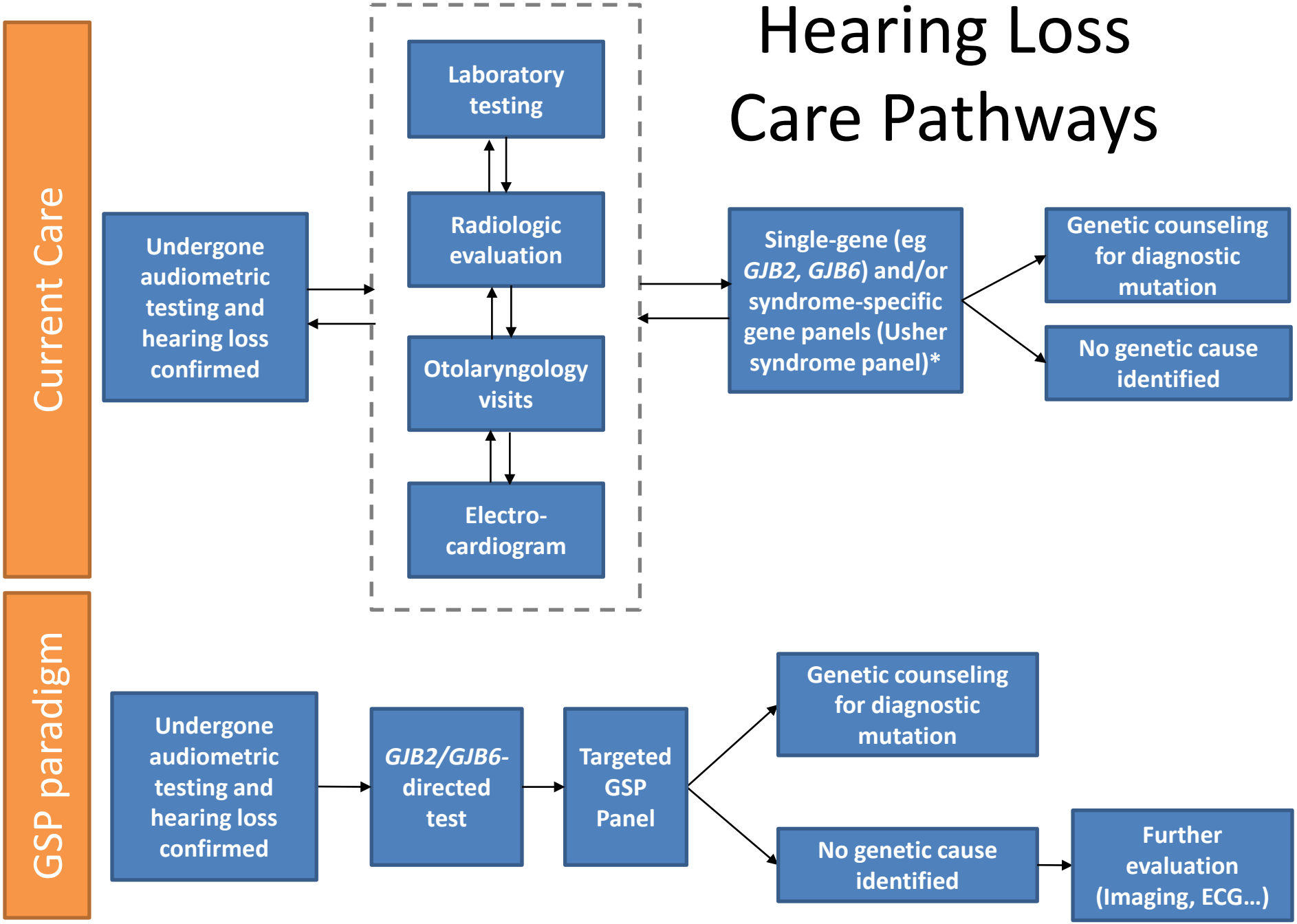
Application

Application	Value Proposition	Cost Offsets
Hearing Loss	Clinicians reduce or avoid "diagnostic odyssey" with panel testing	• Increases yield of mutation testing • Reduces reliance on mix of lab tests, radiological exams, otolaryngologic visits, and EKG
Exome	Gives physicians a tool to better diagnose causes of developmental delay	• Reduces reliance on lab, radiology, single-gene testing and more limited panels • Better diagnostic efficiency reduces overall costs
Targeted, solid organ neoplasm	Example of advanced NSCLC - more clearly differentiates patients for appropriate targeted or non-targeted treatment approaches	• Increases more effective molecular-targeted or conventional therapy determination depending on findings • Increases clinical trial participation • Marginal increase in test cost

Model Summary Page



Hearing Loss Care Pathways

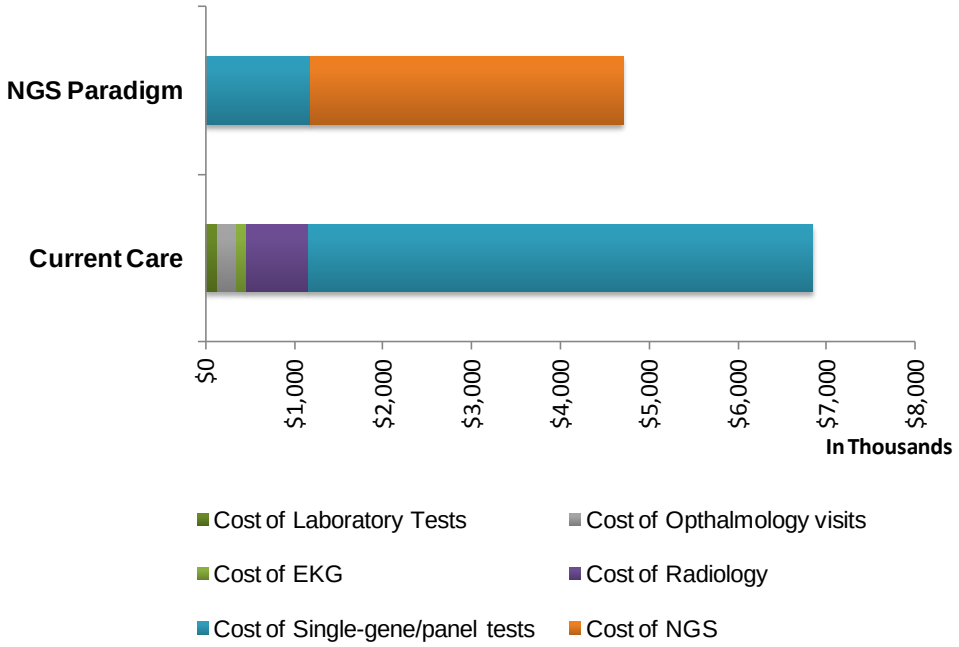


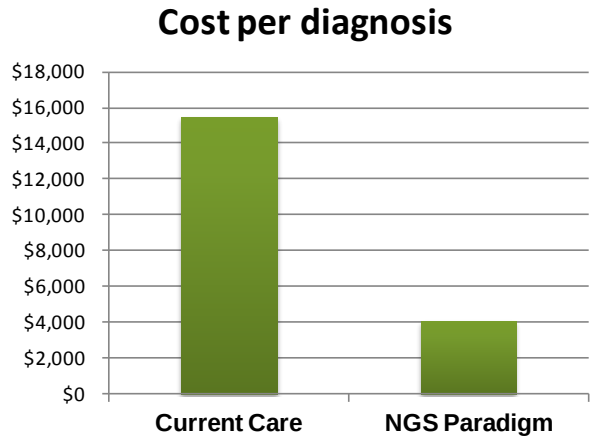
Key Inputs: Hearing loss

Variable	Input	Source
Plan Demographics		
Number of covered Lives	10 million	Representative plan size
Sensorineural Hearing Loss Incidence	0.022%	Census/ASHA/Blanchfield et al, J Am Acad Audiol. 2001.
Number patients with SNHL < 18 years	2,209	Calculations
Standard of Care		
Percent getting Temporal Bone CT	79%	Mafong DD, et al. Laryngoscope, 2002
Percent getting Brain MRI	18%	Mafong DD, et al. Laryngoscope, 2002
Percent getting Renal Ultrasound	79%	Lin JW, et al. Otol Neurotol, 2011
Percent getting ECG	53%	Lin JW, et al. Otol Neurotol, 2011
Percent getting Otolaryngology visits	100%	2007 position statement: Principles and guidelines for early hearing detection and intervention programs
Percent getting GJB2/GJB6 tests	100%	Data from Academic Medical Center
Diagnostic Yield of GJB2/GJB6 testing	20%	Data from Academic Medical Center
Cost of GJB2/GJB6-directed tests	$535	2014 CLFS
Assay Key Inputs		
Test cost	$2,000	Assumption (Model input)
Diagnostic Yield of Panel	40%	Assumption (Model input)

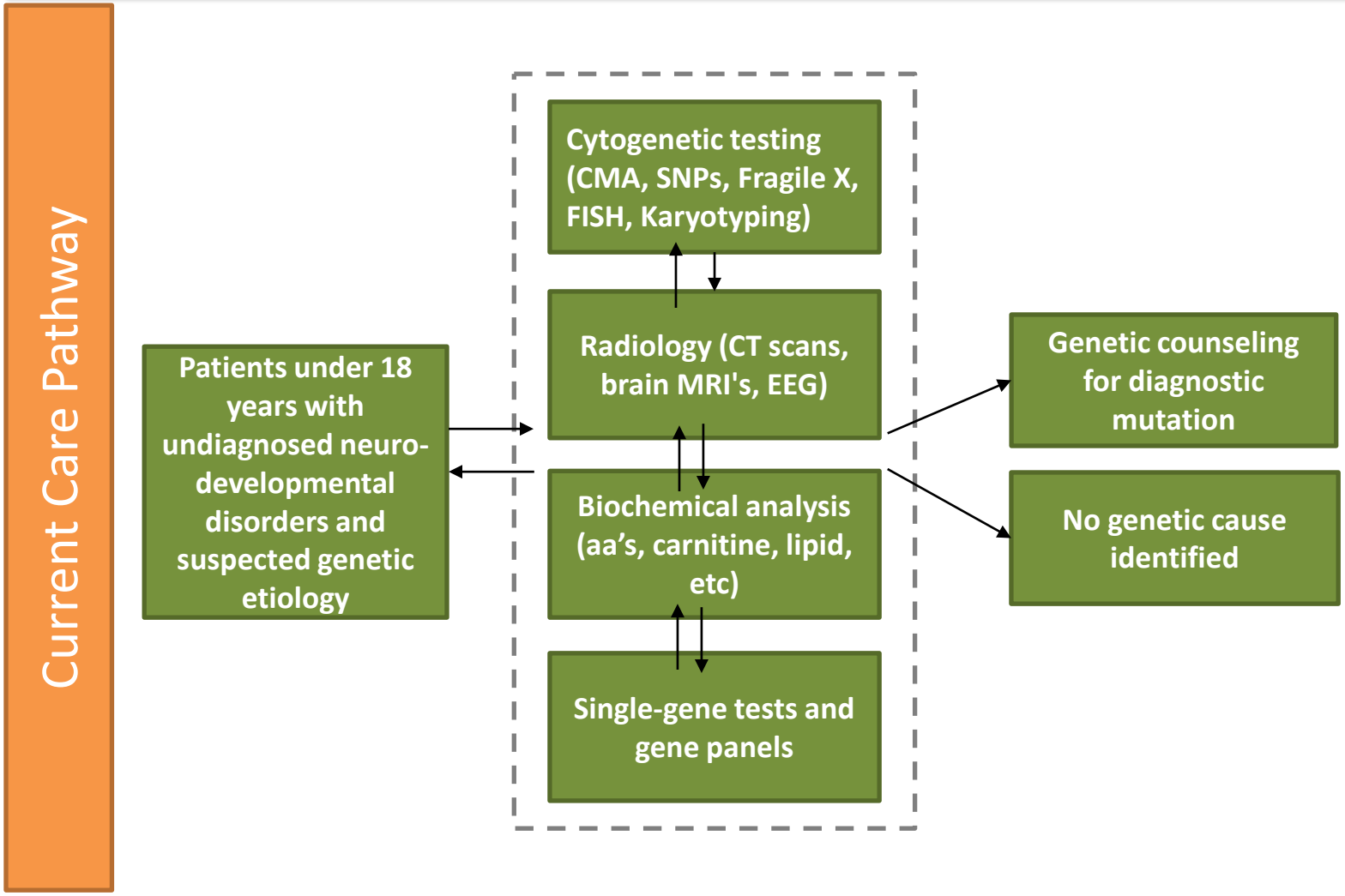
Results: Hearing loss

	Diagnostic Yield	# of Diagnoses	Total Cost	Cost/Diagnosis
Current Care	20.0%	442	$6,845,579	$15,498
GSP Paradigm	52.0%	1148	$4,715,337	$4,106

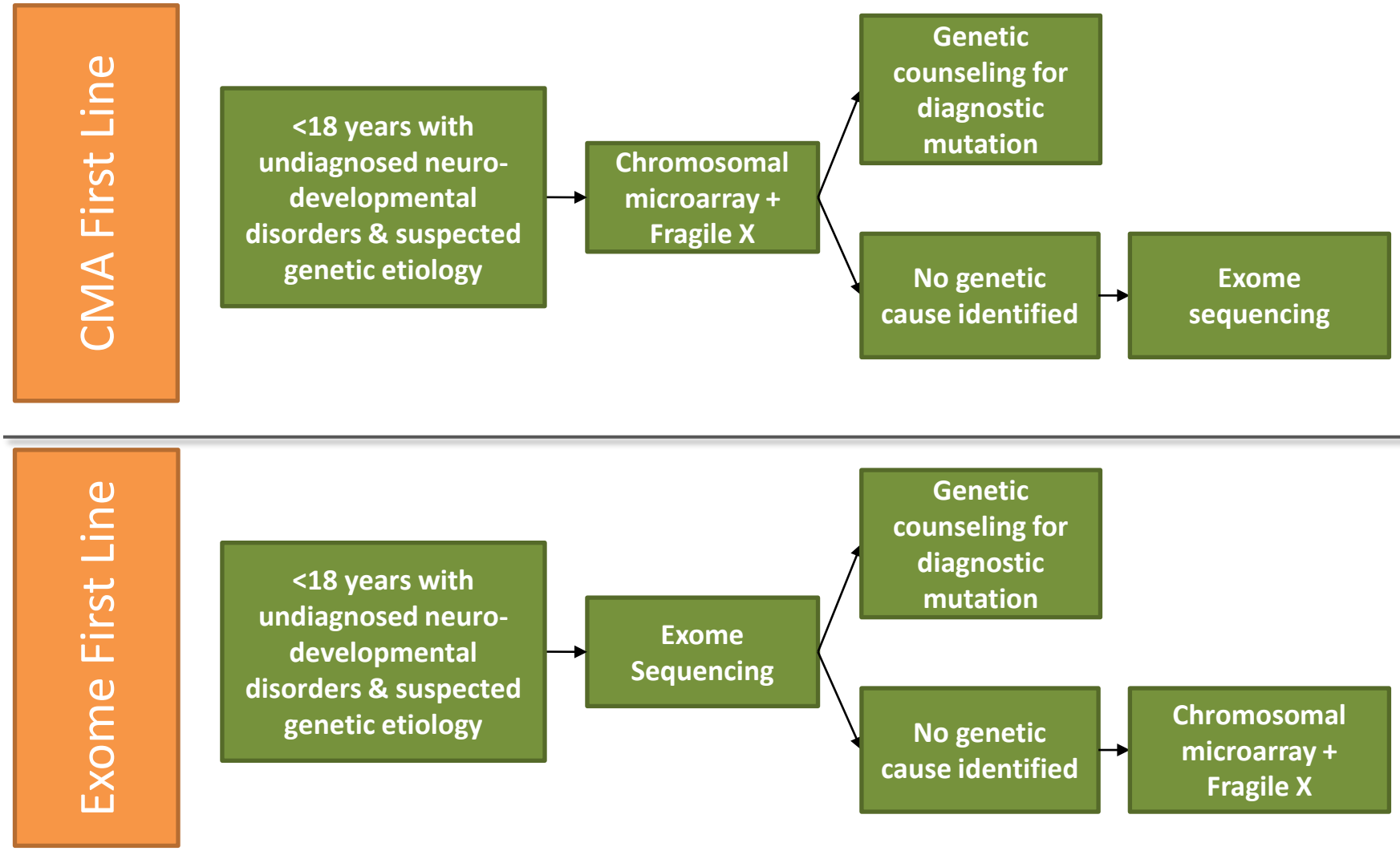




Undiagnosed Neuro-Developmental Disorders Current Care Pathway



Undiagnosed Neuro-Developmental Disorders Exome Sequencing Care Pathway

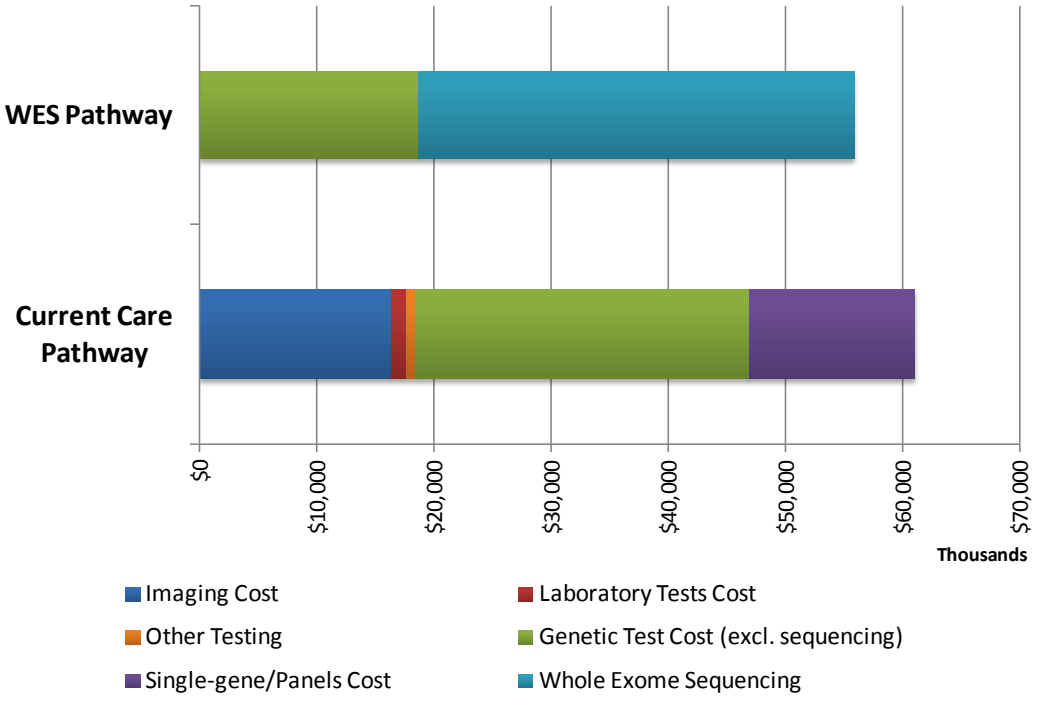


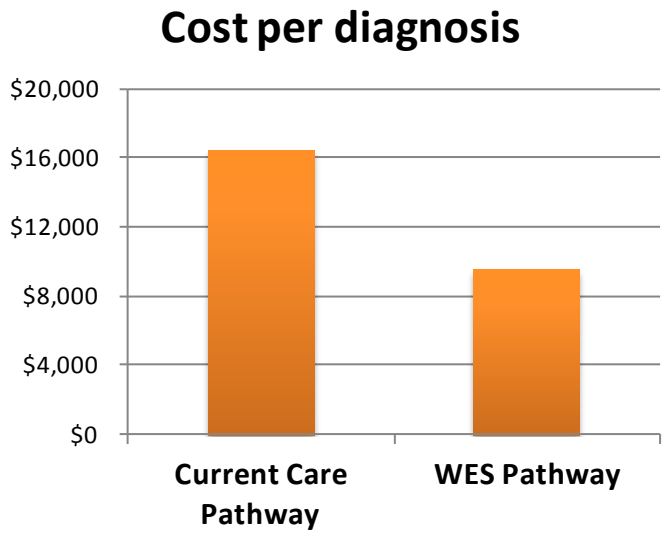
Key Inputs: Exome

Variable	Input	Sources
Plan Demographics		
Number of Covered Lives	1 million	Representative plan size
Percent with neuro-developmental disorder	1.239%	Census/CDC
Number of children with NDD in plan	12,394	Calculations
Standard of Care		
Percent getting CT/MRI	95%	Patient data provided by KOL
Percent getting ECG	29%	Patient data provided by KOL
Percent getting EEG	76%	Patient data provided by KOL
Percent getting ECG	53%	Patient data provided by KOL
Percent getting Biopsies	34%	Data from Academic Medical Center
Percent getting single or panel gene tests	57%	Data from Academic Medical Center
Percent getting CMA & Fragile X	100%	Data from Academic Medical Center
Diagnostic Yield of CMA & Fragile X	25%	Schaefer, Genetics in Medicine 2013
Assay Key Inputs		
Cost of exome sequencing	$3,000	Assumption (Model input)
diagnostic yield of exome sequencing	30%	Srivastwa, Annual of Neurology 2014

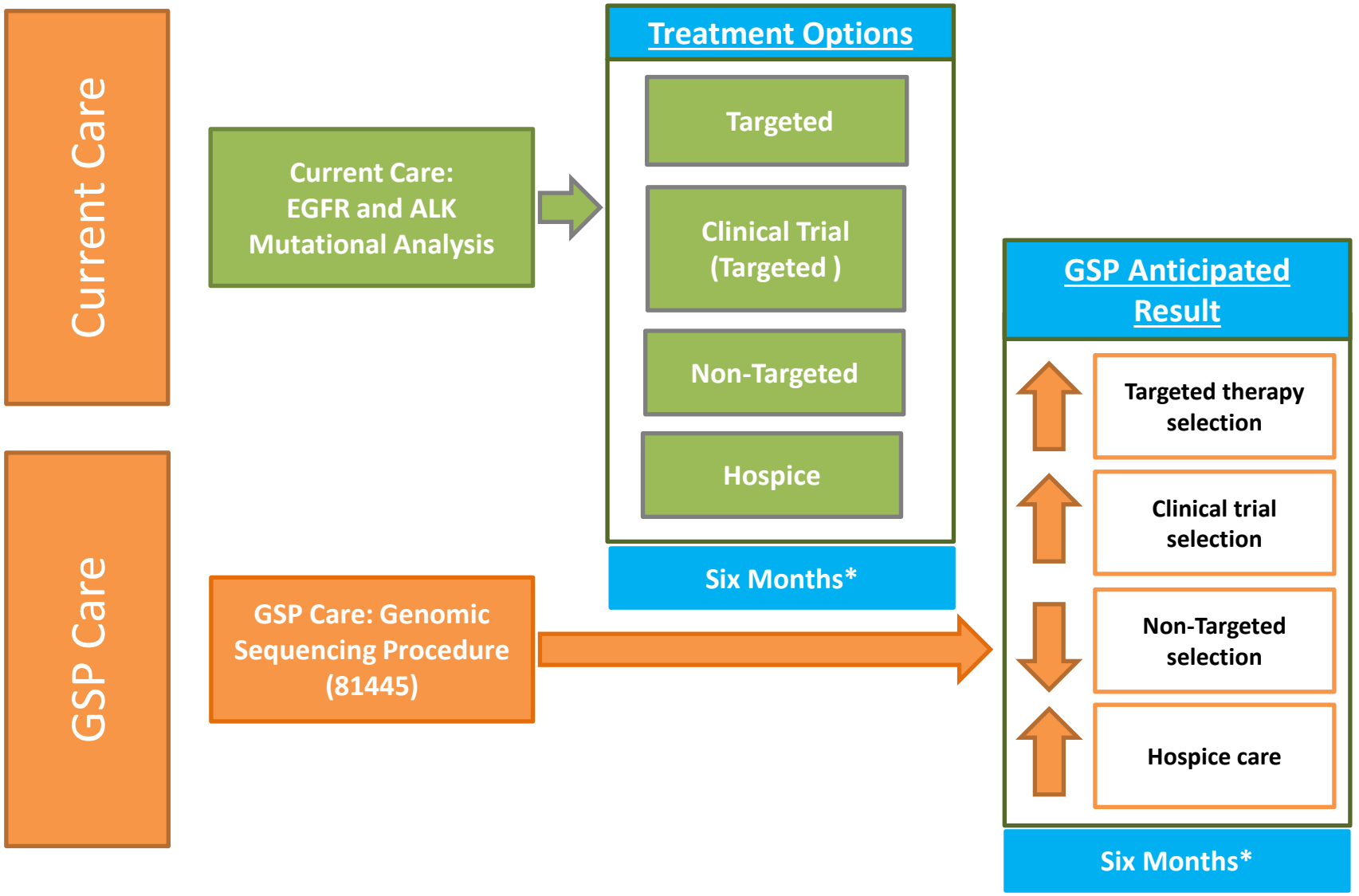
Results Summary: Exome

	Diagnostic Yield	# of Diagnoses	Total Cost (US$)	Cost/Diagnosis (US$)
Current Care Pathway	30.0%	3718	$60,963,556	$16,396
WES Pathway	47.5%	5887	$55,833,275	$9,484





Model Framework: NSCLC

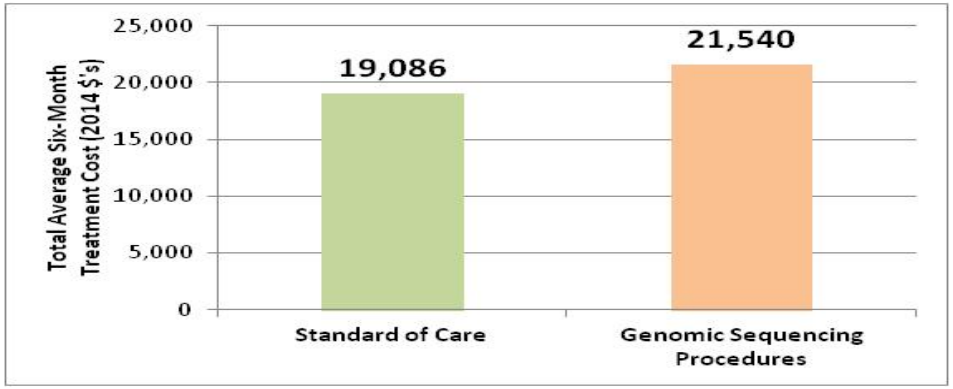


Key Inputs: NSCLC

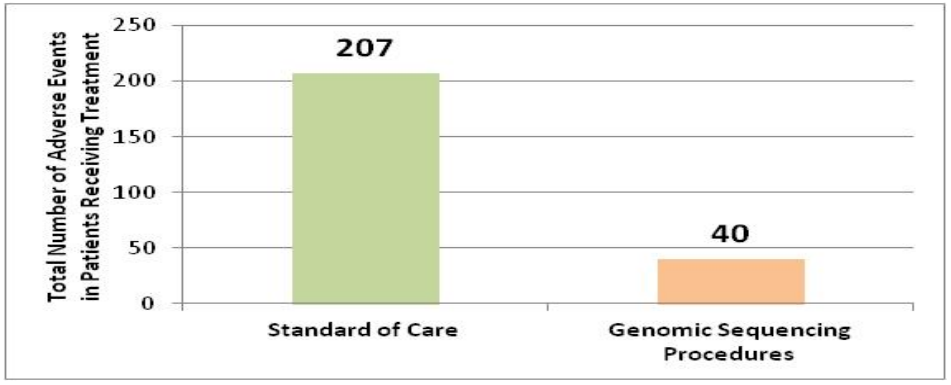
Variable	Input	Sources
Plan Demographics		
# of covered Lives	10 million	Representative plan size
Lung cancer incidence	.07%	Annual lung cancer incidence rate (2014 NCI SEER data) & U.S. Population (Census Bureau)
Percentage of diagnoses at stage IIB/IV	88.2%	Wisnivesky et al. Chest 2005, NCI SEER Stat Fact Sheet 2014
# diagnosed with advanced or metastatic cancer	5,496	Based on plan covered lives, lung cancer incidence rate & percent diagnoses at stage IIIB/IV
Standard of Care		
Treatment Decisions: Targeted therapy Non-targeted therapy Clinical trial Hospice care	 6% 83% 4% 7%	The Cancer Genome Research Network 2014; Pan et al. 2013; NCI Cancer Bulletin 2014; Mattson Jack Treatment Architecture 2007
# Adverse Events in patients receiving treatment	207	Adverse event rates for pharmacologic treatments weighted by treatment utilization percentage
Total months of progression free survival (PFS)	2,540	PFS rates for for pharmacologic treatments weighted by treatment utilization percentages
Total average treatment cost	$19,086	Weighted average of individual treatment decision pathways from published data and KOLs
Average diagnostic testing cost for EGFR + ALK	$467	Medicare Fee Schedule 2014

Result Summary: NSCLC

Total Average Treatment Cost

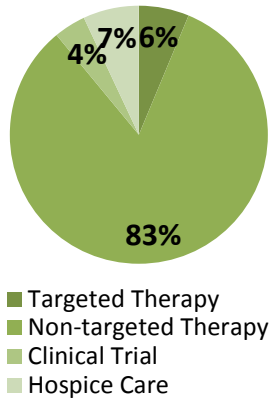


Total Number of Adverse Events

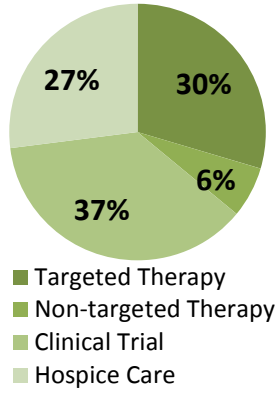


Treatment Decisions

Standard of Care



Genomic Sequencing Procedures



Putting These Tools Into Practice

Template Model Has Structure and Inputs for Completing Micro-cost Models Individually

	Assay Section	Reagents and Disposables (Consumables)							Equipment					Personnel			
	Steps	Consumables	Identifier	Consumable Cost	Qty	Unit	Batch Size	Cost per Step	Equipment Used	Identifier	Equipment Cost	Equipment Time (min)	Cost per Step	Hands On Personnel Time (min)	Personnel Cost per Minute	Personnel Type	Cost per Step
DNA Extraction	DNA is extracted (typically from blood or tumor)																
DNA Quality Control	QC is done to determine the quality of each DNA sample relative to the calibrator. Adjustments may be made by dilution.																
Library Preparation (Pre PCR)	DNA targets are selected by hybridization of strand specific oligonucleotides. Here, oligonucleotide primed extension and ligation takes place. Enrichment steps may vary depending on platform. Some enrichment technologies include the Agilent SureSelect, Roche's SeqCap, RainDance Thunderstorm and Fluidigm's Access Array.																
Library Preparation (Post PCR)	Amplification by PCR adds unique barcodes to samples. Paramagnetic beads are used for cleanup prior to quantification.																
Library Quantification & Normalization	Assessment of the quality and quantity of each library. Libraries are normalized by appropriate dilution.																
Library Denaturing & Pooling	Libraries are combined into a single pool and denatured.																
Sequence Generation	Sequencing may be preformed on a variety of instruments.																
Documentation																	
Initial Data Review/Quality Assessment	Review of BAM file data to ensure correct reads have been made and it is ready for further analysis using pipeline software	Included above							Infrastructure / Institutional Overhead					Lab Tech		0	$ -
Bioinformatics Pipeline Analysis	Analysis of file using bioinformatics software Base-calling occurs to generate sequence reads. These reads are aligned and mapped against a reference sequence. The software may also do variant/genotype calling and annotation.								Custom pipeline		0	120	1 $ -				

					Useful Life	Utilization/W	Useful Life Minutes	Price	Unit Price per minute
								$ 0.07	0.07200
								$ 0.05	0.04800
								$ 0.06	0.06270
								$ 0.05	0.05400
					61152	50%	1834560	$ 7,330.00	0.00400
								$ 0.07	0.07200
								$ 0.00	0.00400
SL189	ethanol, 100%	µL						$ 0.00	0.00330
SL190	ethanol, 70%	µL						$ 0.00	0.00330
EP110	Freezer	10	10	520	3640	87360	50%	2620800	$ 6,871.07	0.00262
EP046	freezer, ultradeep (-70 degrees)	10	10	520	3640	87360	50%	2620800	$ 16,552.00	0.00632

www.ama-assn.org/resources/doc/rbrvs/direct-input-listings.xls

VWR	Descripti	Unit	Useful Life (Y	Useful Life	Utilization Da	Useful Life	Utilization/W	Useful Life Minutes	Price	Unit Price per minute
20170-010	VWR® PCR	Case of 10,000							$ 803.78	0.08038
87004-272	VWR®	Case of 500							$ 50.52	0.10104
89093-448	SCIENCEWA	Pack of 4							$ 12.28	3.07000
82006-622	VWR Tube Strip 8 Well PK120	Case of 1,200							$ 2,589.57	2.15798

Summary

- The cost and health economic models represent a snapshot of current protocols for genomic sequencing procedures
- Goals:
  - Models will be used by laboratories to evaluate their own costs
  - Models will be used to articulate the value and cost of GSP to payer
  - Models will be adapted to reflect innovations in methods and clinical research
- Recommendations for Laboratories
  - Collaborate with clinicians to collect and report evidence for the clinical and economic value of genomic sequencing procedure applications
  - Do not forget to include the cost and value of assay development and the bioinformatics analysis

Committee Members

GSP Pricing Project Oversight Committee:

- Linda Sabatini, PhD, Sub-committee Chair (EAC)
- Janina Longtine,MD (AMP Board)
- Madhuri Hegde, PhD (AMP Board)
- Vivianna Van Deerlin, MD, PhD (AMP Board)
- Jill Hagenkord, MD (EAC)
- Ester Stein (EAC)
- Katherine Tynan, PhD, Project Manager

Economic Affairs Committee Members:

- Aaron D. Bossler, MD, PhD, Co-Chair
- Jan Nowak, MD, PhD, Co-Chair
- Samuel Caughron, MD, Vice-Chair
- Pranil Chandra, DO
- Jill Hagenkord, MD
- Elaine Lyon, PhD
- Richard Press, MD, PhD
- Linda Sabatini, PhD
- Michele Schoonmaker, PhD
- Ester Stein, MBA
- Dara Aisner, MD, PhD

Consultants

- Erika Miller, JD
- Katherine Tynan, PhD

To the Sponsors of This Project: Thank You For Your Generous Support!

If you are interested in assisting AMP's efforts through sponsorship, contact Mary Williams (mwilliams@amp.org).

Thank You

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