COST AND VALUE OF GENOMIC SEQUENCING PROCEDURES

AMP Economic Affairs Committee

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Outline

- Coding for Genomic Sequencing Procedures
- Cost and Value Project Overview
  - Micro-costing
  - Health economic modeling
- Putting these Tools into Practice

Coding for Genomic Sequencing Procedures

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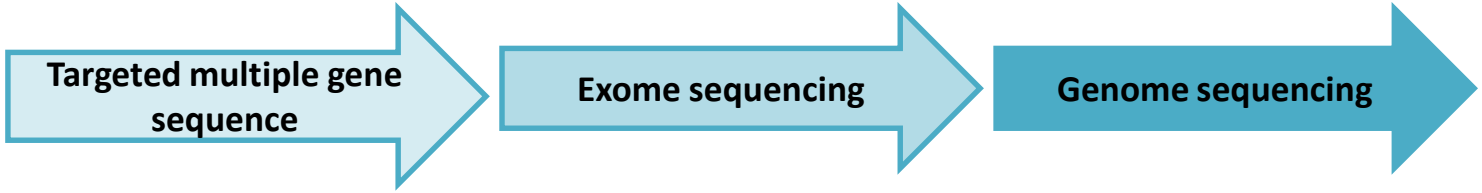
AMP/AMA Created New Genomic Sequencing Procedures for 2015

- Given the advances in clinical applications of next generation sequencing, in 2013 the Association for Molecular Pathology (AMP) proposed the promulgation of a new coding structure to describe genomic sequencing procedures (GSPs).
- The proposed framework categorized GSPs by indication, technical and analytical work involved from least to greatest amount of work:



- The AMA's CPT Editorial Panel accepted a set of new GSP codes to report next generation analysis for 2015 including codes for:
  - Aortic dysfunction
  - Colon cancer panel
  - Nonsyndromic hearing loss
  - X-linked intellectual disability
  - Fetal aneuploidy
  - Whole mitochondrial genome
  - Whole exome and whole genome
  - Targeted solid organ tumor neoplasm somatic mutations

These Codes Describe A Range of Clinical Indications & Applications

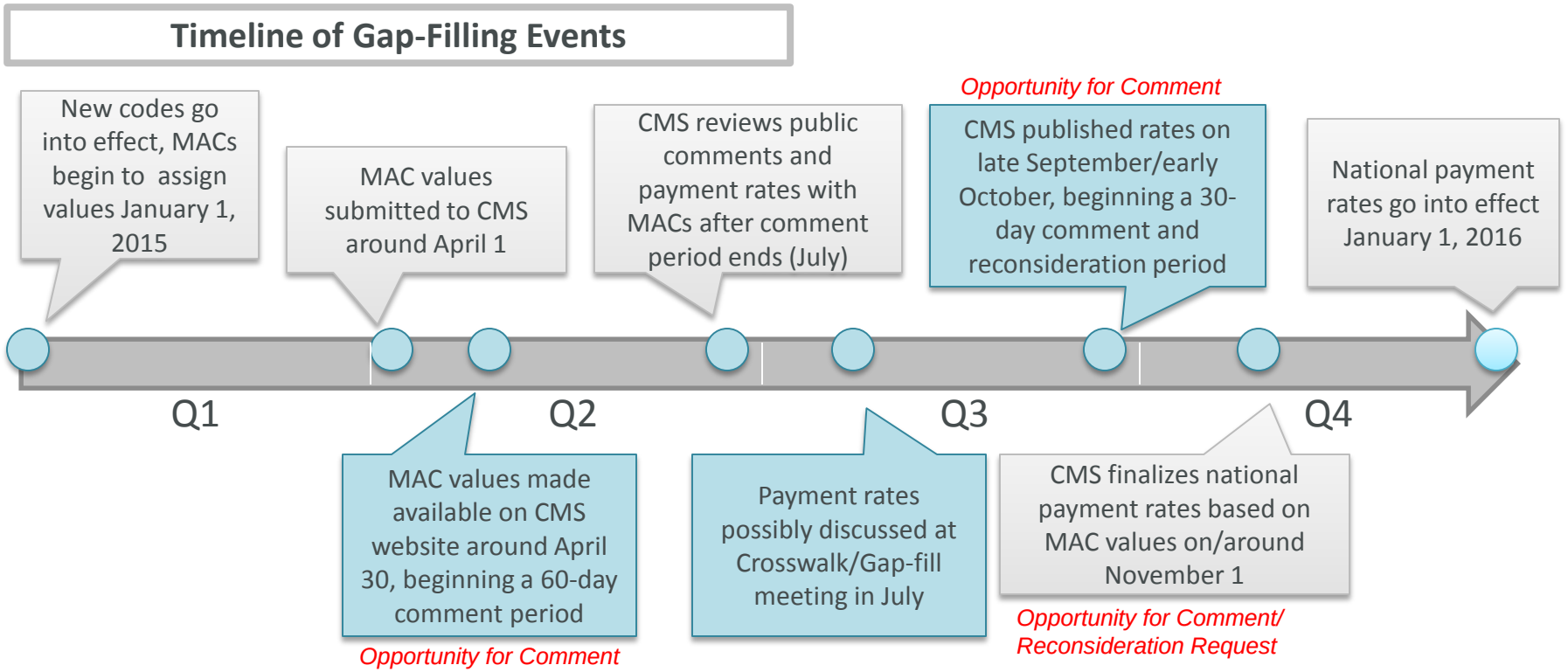
81430 Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); genomic sequence analysis panel, must include sequencing of at least 60 genes, including CDH23, CLRN1, GJB2, GPR98, MTRNR1, MYO7A, MYO15A, PCDH15, OTOF, SLC26A4, TMC1, TMPRSS3, USH1C, USH1G, USH2A, and WFS1

81431 …, **duplication/deletion** analysis panel, must include copy number analyses for STRC and DFNB1 deletions in GJB2 and GJB6 genes

81420 Fetal chromosomal aneuploidy (eg, trisomy 21, monosomy X) genomic sequence analysis panel, circulating cell-free fetal DNA in maternal blood, must include analysis of chromosomes 13, 18, and 21

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

During the Gap-Fill Process, Labs Will Need to Educate Medicare Carriers and Commercial Payers About the Cost and Value of GSP



In October of 2014, CMS announced that it will gap-fill all of the new GSP codes. Therefore, labs will need to work with Medicare Administrative Contractors (MACs) and commercial payers to provide accurate information that reflects the necessary resources needed for these codes. In addition, during 2015, individual plans must decide whether to cover these tests and determine the gap-fill amounts.

The Multiple and Unique Factors of GSP and its Various Potential Clinical Applications Present Challenges in Defining Its Cost and Value

Cost of GSP

Pre-Analytics
- Sample preparation
- Enrichment protocols
- Library preparation

Sequence Analysis
- Technical work
- Different platforms
- Quality control

Result Output/ Interpretation
- Bioinformatics
- Professional expertise
- Clinical data curation
- Data storage

Real World Focus on Clinical Applications

Examples of Possible Values of GSP

Avoidance of a diagnostic odyssey

- A potentially cost-saving replacement for multiple rounds of single gene tests, imaging, biochemistry (e.g., avoidance of serial germ-line testing for hereditary conditions)

Enabling better care through providing more comprehensive information

- A means of securing additional valuable clinical information by examining a broader array of information all at once (e.g., broad tumor panels)

Next generation sequencing enables a shift from single gene tests to multiple gene panels and/or whole exome/genome sequencing. The full implications of having this ability are not yet fully understood.

Cost and Value Project Overview

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AMP Assumed a Leadership Role to Educate Labs on the Importance of Understanding this Process by Completing a Cost and Value Assessment Project

Association for Molecular Pathology

Cost-Base of GSP	Value-Base of GSP
• Objective: Help define the actual real world cost of GSP by a typical GSP lab so that it can be clearly articulated to payers • Examine the true cost of testing for different types of GSP applications • Includes, pre-analytics, sequencing, bioinformatics, and reporting	• Objective: Create tools for defining health economic impact so that labs can use to talk about the value of GSP applications • Analyze the health economic impact of GSP testing in different clinical areas

- **AMP retained two expert groups, Tynan Consulting and Boston Healthcare Associates, to organize and complete the project in mid 2014.**
- **Obtained industry Support from BioReference Laboratories, Roche, Agilent and BD**
- **AMP completed this initiative in February 2015.**

AMP Selected Three Applications Areas Which Represent The Range of GSP Applications and Can be Used as Templates for Further Analyses

- Defining the entire range of clinical applications of GSPs would be too difficult for any one single organization
- Micro-costing of GSP, which provides a baseline estimate for either the most costly or least costly current GSP procedures
- AMP's objective was to create tools and define best practices that can be used as a template for estimating the cost basis of GSP services provided by your lab.
- Define essential types/categories of supportive health economic modeling by providing examples

Project Relied Heavily on Support from Labs that Perform GSPs and KOLs That Use GSPs in Practice

Work Approach Overview

Cost-Base of GSP	Value-Base of GSP
• Defined structure of summary and detailed models • Secured test protocols (SOPs) from 13 labs that are performing GSPs • Conducted site visits with some of these labs • Aggregating data from sites/completing models	• Conducted numerous KOL clinician/HE interviews • Created draft versions of each of the three models • Source additional inputs/reviewing drafts with KOLs • Possible publications in peer-reviewed journals

Cost and Value Project Overview: Micro-Costing

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Why Micro-Costing?

- Allows for a sophisticated, comprehensive articulation of the actual costs associated with performing a complex assay
- Similar to a RUC/RVU analysis, which is done for CPT codes located on Physician Fee Schedule
- Reflects data from many different laboratories performing same assay but in different ways
- Utilizes entire laboratory protocol to consider all aspects of the test (e.g., labor, professional labor, disposable costs, amortized overhead costs, etc.)
- Allows us to convert concepts like bioinformatics, medical curation/reporting, data storage, into tangible per test dollar values
- Sources linked to either supplier cost inputs, Medicare RUC inputs, or VWR

A key objective is to provide a uniform comprehensive transparent cost evaluation.

Micro-Cost Analysis Focused on Specific CPT Codes

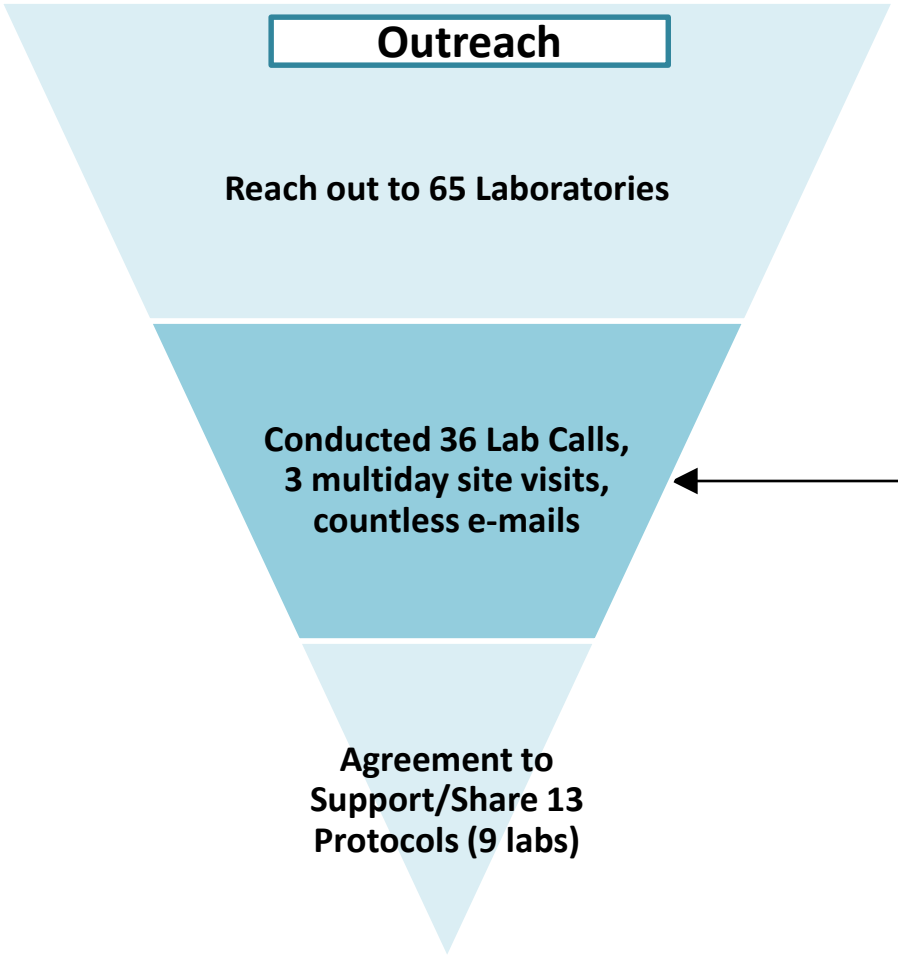
Code	Description
81430	Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); genomic sequence analysis panel, must include sequencing of at least 60 genes, including CDH23, CLRN1, GJB2, GPR98, MTRNR1, MYO7A, MYO15A, PCDH15, OTOF, SLC26A4, TMC1, TMPRSS3, USH1C, USH1G, USH2A, 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)
81415	Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis
81416	sequence analysis, each comparator exome (eg, parents, siblings) (List separately in addition to code for primary procedure) *(Use 81416 in conjunction with 81415)*
81417	re-evaluation of previously obtained exome sequence (eg, updated knowledge or unrelated condition/syndrome)
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 is Designed to Capture the Range of Different Areas Which Reflect Assay Costs

Application	Description
Cost of Consumables/Supplies	Pricing for consumables and supplies such as pipettes, reagents, etc.
Equipment	Use of equipment associated with protocol including pre-analytics and sequencing platforms Usually amortized 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	Amount of hands-on time by laboratory personnel and those involved in creating/draft test reports (analysts, laboratory directors)
Validation, Maintenance, Overhead	Time and cost associated with preparing and keeping the assay ready for clinical use

We collected the specific inputs from the protocols and during calls/meetings with laboratory personnel and collected cost data from CMS, VWR, and vendors.

AMP Reached Out to a Wide Array of Labs to Find Those That Were Well-Qualified to Participate in the Project



Micro-costing

- Objective was to identify 3-5 laboratories per assay category (tumor, targeted genetics panel, whole exome)
- Secure 13 protocols from labs which are performing testing
- Labs are representative of "typical" laboratories
  - Performing at least one run 5+ sample per week
  - Been doing testing for at least 6 months
- Capture "typical" clinical diagnostic workflows with a range of platforms (e.g., MiSeq, Ion Torrent)

The Micro-Cost Analysis Represents a Range of Offerings and Platform Types Used by Both Academic Medical Centers and Commercial Labs

Lab Type	Test Offering	Platform
AMC	Tumor panel (<50 genes)	Ion Torrent
Commercial	Tumor panel (<50 genes)	Ion Torrent
AMC	Tumor panel (<50 genes)	Ion Torrent
AMC	Tumor panel (<50 genes)	MiSeq
AMC	Tumor panel (<50 genes)	MiSeq
Commercial	Tumor Panel (>50 genes)	MiSeq
AMC	Targeted genetics panel	HiSeq
AMC	Hearing loss	HiSeq
Commercial	Hearing loss	HiSeq
AMC	Targeted genetics panel	MiSeq
AMC	Whole exome	HiSeq
Commercial	Whole exome	HiSeq
AMC	Whole exome	NextSeq

Split between tumor panels (n=6) and genetics assays (n=7). Good mix of platforms (Ion torrent=3, MiSeq=4, HiSeq=5, NextSeq=1)

Micro-Costing Exercise Produced Two Types of Information

1) 13 Detailed Models (one per lab)
   - The detailed protocol-level accounting of each protocol step and aggregation of cost inputs
   - Not available to public due to confidentiality agreements with labs

2) Micro-Cost Analysis Aggregate Data Page
   - Data aggregation page consisting of blinded data for each lab
   - Available to the public

Example: Detailed Micro-Costing Model

Individual Protocol Steps

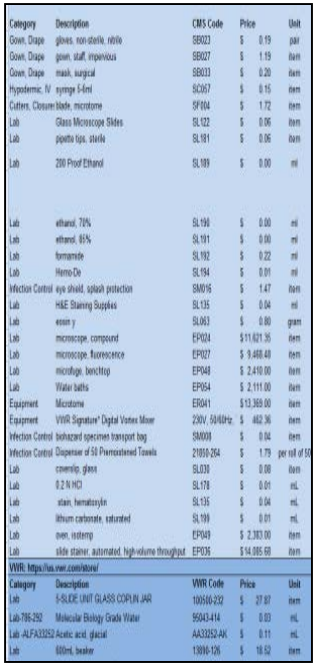
Supplies/ Consumables

Reagent/ Equipment List

Personnel Time/Cost

	Materials from kit	Qty (ie mL when app.)	Sample Size	Additional materials	Qty (in mL when app.)	Samples	Equipment Time (min)	Equipment Cost	Equipment Cost per min	Total Equip Cost per step	Hands Off Time (min)	Hands On Personnel Time per unit (min)	Unit Size	Unit	Personnel Type	Time Factor	Personnel Cost (min)	Total Personnel Cost (per step)
Thaw the appropriate number of DNase Stock tubes																		
Add the calculated DNase Stock and Buffer RDD volumes to an appropriately sized tube and mix by gently pipetting up and down 2 to 3 times.										$ 0.77								$ 0.97
				Pipette P1000	1		1	$ 309.00	$ 0.00	$ 0.00		2	1	run	Med Tech	1	$ 0.48	$ 0.97
				Pipette Tip P1000	1		-	$ 0.14	$ -	$ 0.14								
				Pipette P200	1		1	$ 309.00	$ 0.00	$ 0.00								
				Pipette Tip P200	1		-	$ 0.11	$ -	$ 0.11								
				2mL tube	1		-	$ 0.52	$ -	$ 0.52								
Add 350 µL of Buffer RWT into each of the RNA Elution Spin Columns.										$ 2.00								$ 2.54
												5.25	1	run	Med Tech	1	$ 0.48	$ 2.54
Close each column lid gently.																		
Centrifuge for 15 seconds at ≥10,000				Centrifuge	1		0.25	$ 2,410.00	$ 0.01	$ 0.00	0.25	0.5	1	run	Med Tech	1	$ 0.48	$ 0.36
				Pipette P1000	1	14	2	$ 309.00	$ 0.00	$ 0.03								
				Pipette Tip P1000 (controls)	2		-	$ 0.14	$ -	$ 0.28								
				Pipette Tip P1000 (samples)	1	12	-	$ 0.14	$ -	$ 1.69								
Dispose of the filtrate into a designated guanidine waste																		
Retain the collection tube for the next																		
Add 80 µL of DNase Working Mix onto each of the RNA Elution Spin Column membranes.										$ 2.00								$ 0.97
				P200 Pipette	1	14	2	$ 309.00	$ 0.00	$ 0.03		2	1	run	Med Tech	1	$ 0.48	$ 0.97
				Pipette Tip P1000 (controls)	2		-	$ 0.14	$ -	$ 0.28								
				Pipette Tip P1000 (samples)	1	12	-	$ 0.14	$ -	$ 1.69								
Incubate at 20 to 25°C for 15 ± 1.																		
											15		1	run	Med Tech	1	$ 0.48	$ 7.25
Add 350 µL of Buffer RWT into each of the RNA Elution Spin Columns.										$ 1.97								$ 3.82
				P1000 Pipette	1	14	2	$ 309.00	$ 0.00	$ 0.00		6.25	1	run	Med Tech	1	$ 0.48	$ 3.38
				Pipette Tip P1000 (controls)	2		-	$ 0.14	$ -	$ 0.28								
				Pipette Tip P1000 (samples)	1	12	-	$ 0.14	$ -	$ 1.69								

AssumptionsKey | Steps | CostPerKitLookUp | RUCLookUp | Dissection | H&E Stain | NFR | Personnel | Aliquot Calc | Inventory of placeholders



Category	Description	CMS Code	Price	Unit
Gown, Drape	gloves, non-sterile, nitrile	SB023	$ 0.19	pair
Gown, Drape	gown, staff, impervious	SB027	$ 1.19	item
Gown, Drape	mask, surgical	SB033	$ 0.20	item
Hypodermic, IV	syringe 5-6ml	SC057	$ 0.15	item
Cutters, Closure	blade, microtome	SF004	$ 1.72	item
Lab	Glass Microscope Slides	SL122	$ 0.06	item
Lab	pipette tips, sterile	SL181	$ 0.06	item
Lab	200 Proof Ethanol	SL189	$ 0.00	ml
Lab	ethanol, 70%	SL190	$ 0.00	ml
Lab	ethanol, 95%	SL191	$ 0.00	ml
Lab	formamide	SL192	$ 0.22	ml
Lab	Hemo-De	SL194	$ 0.01	ml
Infection Control	eye shield, splash protection	SM016	$ 1.47	item
Lab	H&E Staining Supplies	SL135	$ 0.04	ml
Lab	eosin y	SL063	$ 0.80	gram
Lab	microscope, compound	EP024	$ 11,621.35	item
Lab	microscope, fluorescence	EP027	$ 9,468.48	item
Lab	microfuge, benchtop	EP048	$ 2,410.00	item
Lab	Water baths	EP054	$ 2,111.00	item
Equipment	Microtome	ER041	$ 13,369.00	item
Equipment	VWR Signature® Digital Vortex Mixer	230V, 60/40Hz	$ 462.36	item
Infection Control	biohazard specimen transport bag	SM008	$ 0.04	item
Infection Control	Dispenser of 50 Premoistened Towels	21856-264	$ 1.79	per roll of 50
Lab	coverslip, glass	SL030	$ 0.08	item
Lab	0.2 N HCl	SL178	$ 0.01	mL
Lab	stain, hematoxylin	SL135	$ 0.04	mL
Lab	lithium carbonate, saturated	SL199	$ 0.01	mL
Lab	oven, isotemp	EP049	$ 2,383.00	item
Lab	slide stainer, automated, high-volume throughput	EP036	$ 14,085.68	item
VWR: https://us.vwr.com/store/				
Category	Description	VWR Code	Price	Unit
Lab	5-SLIDE UNIT GLASS COPLIN JAR	10556-222	$ 27.87	item
Lab-786-292	Molecular Biology Grade Water	95043-414	$ 0.03	mL
Lab-ALFA33252	Acetic acid, glacial	AA33252-AK	$ 0.11	mL
Lab	600mL beaker	13916-126	$ 18.52	item

Cost inputs sourced from CMS, VWR, vendors

Micro-Cost Summary Data Output

Copyright © 2015. Association for Molecular Pathology. All Rights Reserved.	Version 0.9 Beta	Tumor Less than 50 Genes					Tumor Greater than 50 Genes	Targeted Genetics Panel				Whole Exome		
DRAFT	2/12/2015													
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	MiSeq	MiSeq	Illumina MiSeq	Illumina MiSeq	Illumina HiSeq	Illumina HiSeq	Illumina HiSeq	Illumina HiSeq	Illumina HiSeq	NextSeq
Bioinformatics/Data Analysis/Report Creation		Director Review Custom Pipeline	Director Review Custom Pipeline	Director Review Custom Pipeline	Director Review Custom Pipeline	Director Review Commercial Pipeline	Director Review Commercial Pipeline	Director Review Custom Pipeline	Director Review Custom Pipeline	Group Review Custom Pipeline	Director Review Custom Pipeline	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	35	25	276	175	45	10	35
	Report Development	45	60	20	30	15	53	45	17	30	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	$ 153.14	$ 163.08	$ 477	$ 465.84	$ 195.59	$ 157.32	$ 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	$ 577.39	$ 1,348	$ 314.03	$ 1,047.64	$ 1,343.47	$ 1,890.27	$ 1,337.60	$ 3,388.18	$ 2,428.45

Key Findings

- Current offerings in tumor panels:
  - Mostly users of targeted panels are currently offered as RUO kits (e.g., Ion AmpliSeq Cancer Hotspot Panel , TruSeq Amplicon Panel)
  - These methods do not typically include duplications/deletions and are hotspot PCR approaches rather than target capture approaches providing full coverage and do not assess normal versus tumor to sort out somatic versus germ-line mutation.

- Current offerings in targeted genetics tests:
  - Duplication/deletions are typically assessed via another technology (microarray, PCR, FISH) and are therefore not included in micro-costing.

- Current offerings in exome:
  - Labs performing these tests have started relatively recently and are focused on the "medical" exome (variations with known significance).

The micro-costing exercise did not assess assay quality. The objective is to capture the resources required to perform existing GSPs.

Key Findings

- Whole exome and broad tumor panels are the most expensive applications, targeted tumor panels the least expensive
- Key cost drivers: reagents (kit cost), equipment, reporting personnel time
- Each protocol unique and requires multiple instruments
- Observed strong variation in validation and assay development costs when labs offer V2 as opposed V1
- Costs likely to change once kits are FDA approved

Reasons for Cost Differences

- Number of assays equipment and pipeline used for translates to important cost differences (i.e., greater economy of scale when same tool can be used for multiple purposes)
- Batch size
- Library pooling
- Type of equipment used
- Group reviews cost significantly more than reviews done with mainly software

Key Findings: Summary

- Average cost of <50 tumor: $691.07
  - Range: $577.99-907.82
- Average cost of targeted panel: $1,450.35
  - Range: $914.03-$1,949.47
- Average cost of exome: $2,404.74
  - Range: $1,397.60-$3,388.18

Average Cost by Step

- Sample Type/DNA Extraction: $15.17
- Library Prep: $296.73
- Sequencing:$469.49
- Bioinformatics/Data Reporting: $375.26
- Validation/Maintenance/ Overhead: $260.21

Applicability to GSP Codes - Genetic Disorders

- We focused on hearing loss as an example of a targeted panel for genetic panel.
- The micro costing model encompasses all of the pre and post analytic steps for these tests and may be extrapolated to other GSP codes for other genetic disorders that use a similar assay design.
- In some cases, labs were conducting these assays as part of a single pan-disorder panel which means the methodology would remain the same but only reporting times may be different.
- The duplication/deletion codes were not largely used by the laboratories involved in the microcosting project and will need future analysis.

Code	Description
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
81431	duplication/deletion analysis panel, must include copy number analyses for STRC and DFNB1 deletions in GJB2 and GJB6 genes
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)

Exome GSP Codes

- The micro-costing model is built to capture the entire process of running either a patient or parent sample: codes 81415 and 81416
- When re-evaluating samples (code 81417), the up-front, non-bioinformatics portions of the detailed micro-costing model may be concealed and the back-end analytics segment of the model can be used to calculate the cost of re-evaluation.

Exome GSP

Code	Description
81415	Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis
81416	sequence analysis, each comparator exome (eg, parents, siblings) (List separately in addition to code for primary procedure) *(Use 81416 in conjunction with 81415)*
81417	re-evaluation of previously obtained exome sequence (eg, updated knowledge or unrelated condition/syndrome)

Somatic Mutation GSP Codes

- We focused on solid tumor neoplasms as an example.
- All labs we engaged where doing panels with <50 genes (single nucleotide mutation only), therefore we have the strongest information in that area.
- To the extent the workflow remains similar for larger gene panels, hematolymphoid may be extrapolated to other GSP codes for other somatic mutation approaches.

Code	Description
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

Cost and Value Project Overview: Health Economic Modeling

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Health Economic Modeling of GSP Assays

Objectives

- Estimate and compare the cost-utility of next generation sequencing technology with that of current standard testing and medical intervention algorithms, so that their value proposition is fully understood.

Design Principles

1) Transparency and unbiased data presentation (referenced assumptions)
2) Focus on value of test to key stakeholder hospital, hospital system, payer in terms of avoided costs (e.g. procedures, visits, imaging, side effects, adverse events)
3) Ground the analysis in the realities of clinical care
4) Dual-layered (simple presentation supported by extensive underlying detail)
5) Flexibility

HE Modeling Steps

1) Define current diagnostic and treatment pathways
   - Identify evidence and gaps through literature review and KOL consultation
2) Develop and program US Payer-oriented Budget Impact Model
3) Develop and submit abstract and manuscript for presentation and publication

We leveraged information about the contrast between current care and GSP care patterns from KOL discussion/literature review, developed a comprehensive model, and hope to eventually present them in abstract/KOL supported publications.

Each Model Presents Unique Clinical Advantages and Provides a Structural Model for Future Applications Using Different Inputs

Application	Value Proposition	Cost Offsets
Hearing Loss Panel	GSP allows clinicians to avoid a diagnostic odyssey	• Reduces reliance on mix of laboratory tests, radiological exams, opthamologic visits, and EKG • Reduces cost of diagnosis and increases yield versus single gene tests
Whole Exome	GSP (+CMA) gives physicians a tool to better diagnose causes of development delay	• Reduces reliance on lab, radiology, single-gene testing and more limited panels • Better diagnostic efficiency reduces overall costs
Tumor Panel	GSP in advanced NSCLC shifts patients from non-targeted therapies to more appropriate treatment approaches	• Decreases non-targeted therapy use • Increases targeted therapy use, clinical trial, and hospice care • Marginal increase in cost but adds clinical benefit (avoided adverse events, increased PFS)

Models based on limited data from key centers that are at forefront of testing, but we believe this information can be expanded over time. KOL supporters are a mix of clinical experts and health economists.

Example of Model Summary Page

Background

Care Pathways

Workup Inputs

Cost Inputs

Model Summary

Budget Impact Model: Summary

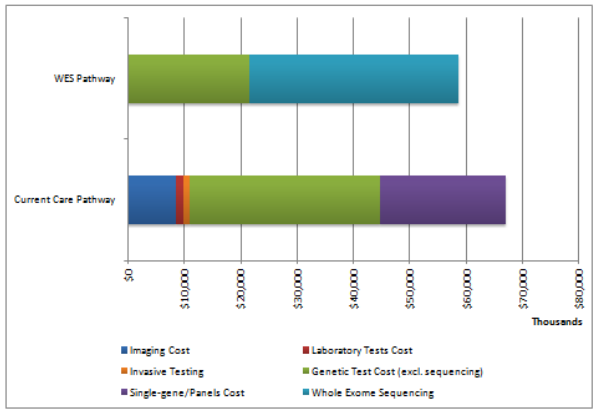
	Model input	Default	Source
Number of plan members	1,000,000	1,000,000	Input
Percent of members that are children with neuro-developmental disorders	1.239%	1.239%	Census/CDC (See Prev)
Number of children with NDD in plan	12,394	12,394	Calculation

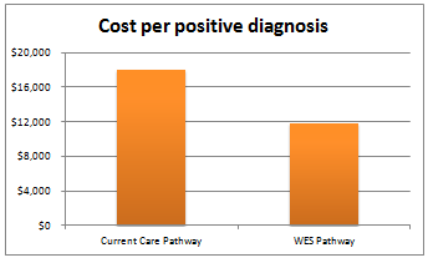
	Model input	Default	Source
Cost of WES	$3,000	$1,500	Assumption
Incremental diagnostic yield of WES	20%	20%	(2)

Restore to Default

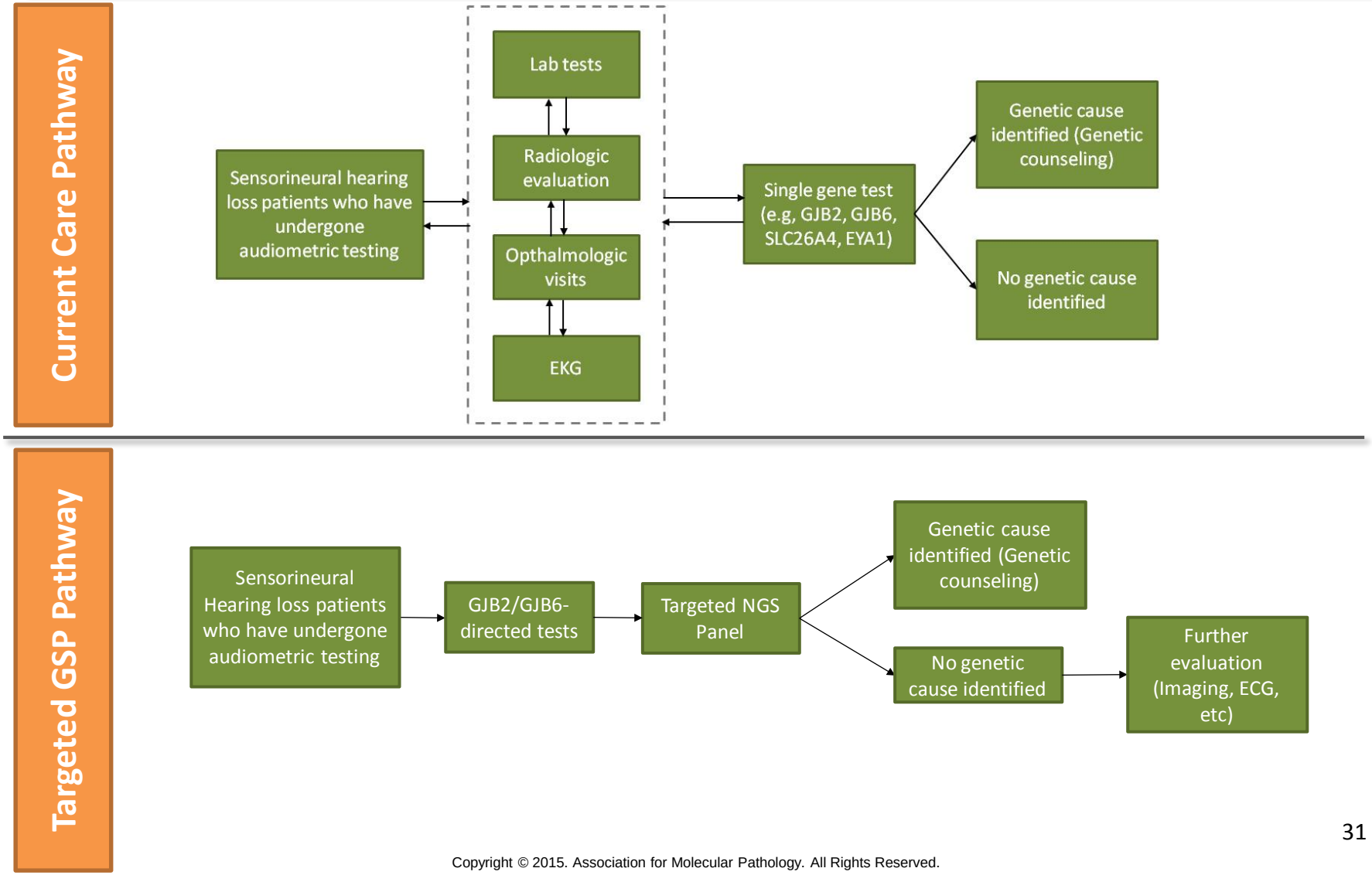
	US$		
Cost Category	Current Care Pathway	WES Pathway	Cost-saving (US$)
Imaging Cost	$8,594,853	$0	$8,594,853
Laboratory Tests Cost	$1,129,236	$0	$1,129,236
Invasive Testing	$1,153,302	$212,390	$940,912
Genetic Test Cost (excl. sequencing	$33,751,406	$21,317,033	$12,434,373
Single-gene/Panels Cost	$22,428,918	$0	$22,428,918
Whole Exome Sequencing	$0	$37,180,872	-$37,180,872
Total Cost of Diagnosis	**$67,057,716**	**$58,710,294**	**$8,347,422**

Outcomes	Overall Diagnostic Yield	# of positive diagnoses	Total Cost (US$)	Cost/diagnosis (US$)	
Current Care Pathway	30.0%	3718	$67,057,716	$18,036	(1)
WES Pathway	40.0%	4957	$58,710,294	$11,843	(3)





Model Summary: Hearing Loss

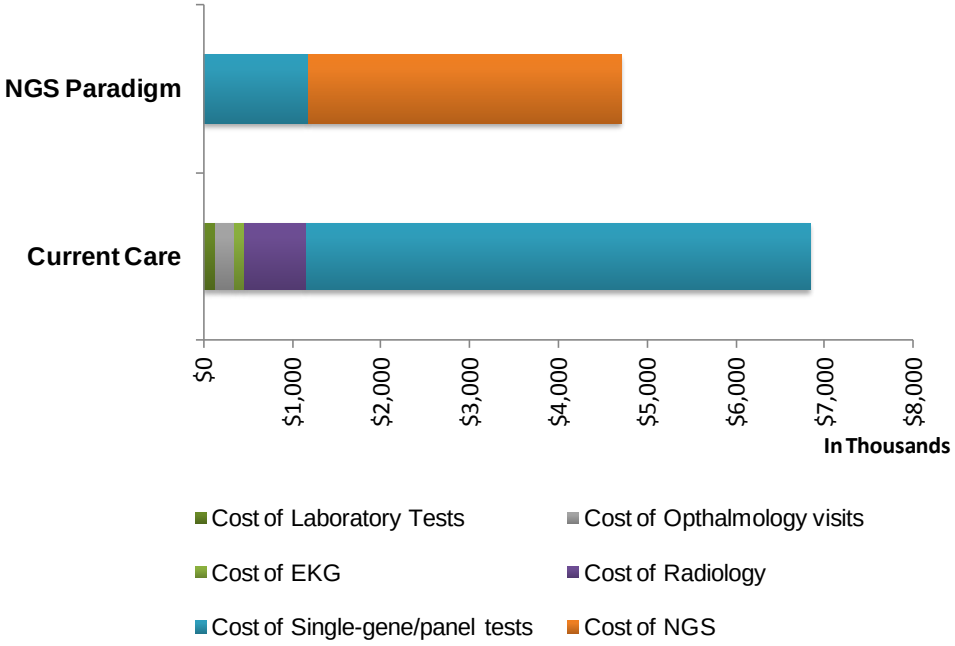


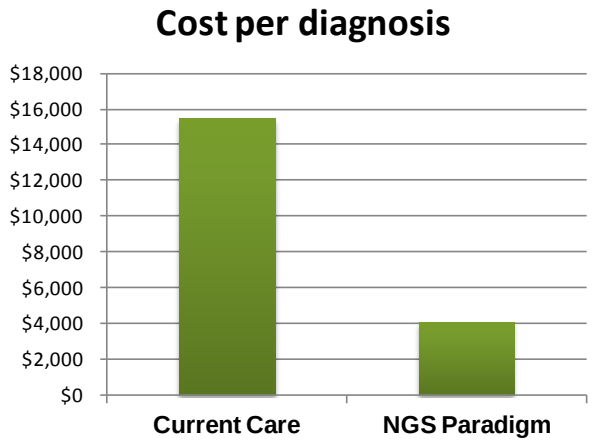
Key Inputs: Hearing Loss

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

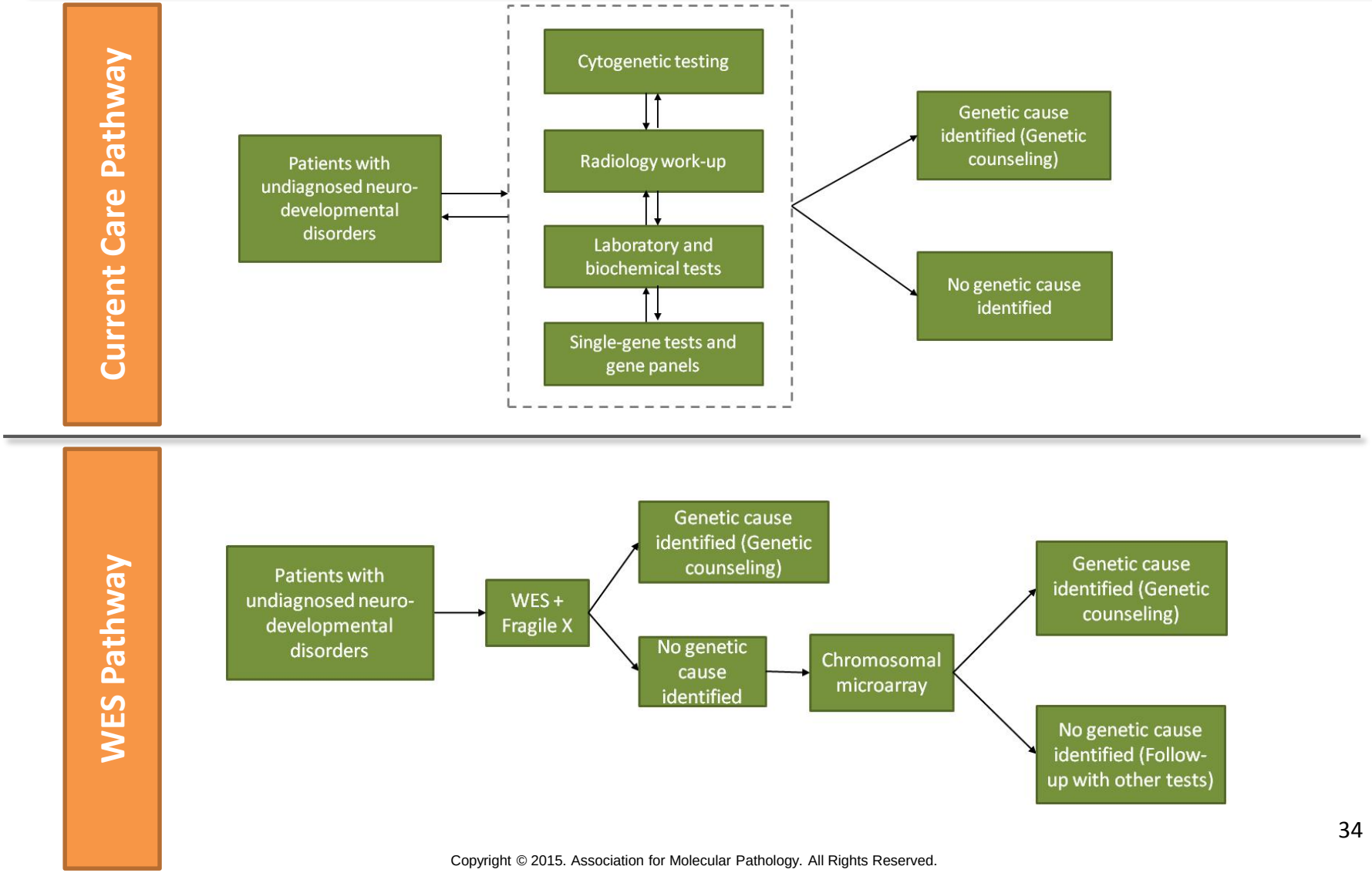
Results Summary: Hearing Loss

	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





Model summary: Exome

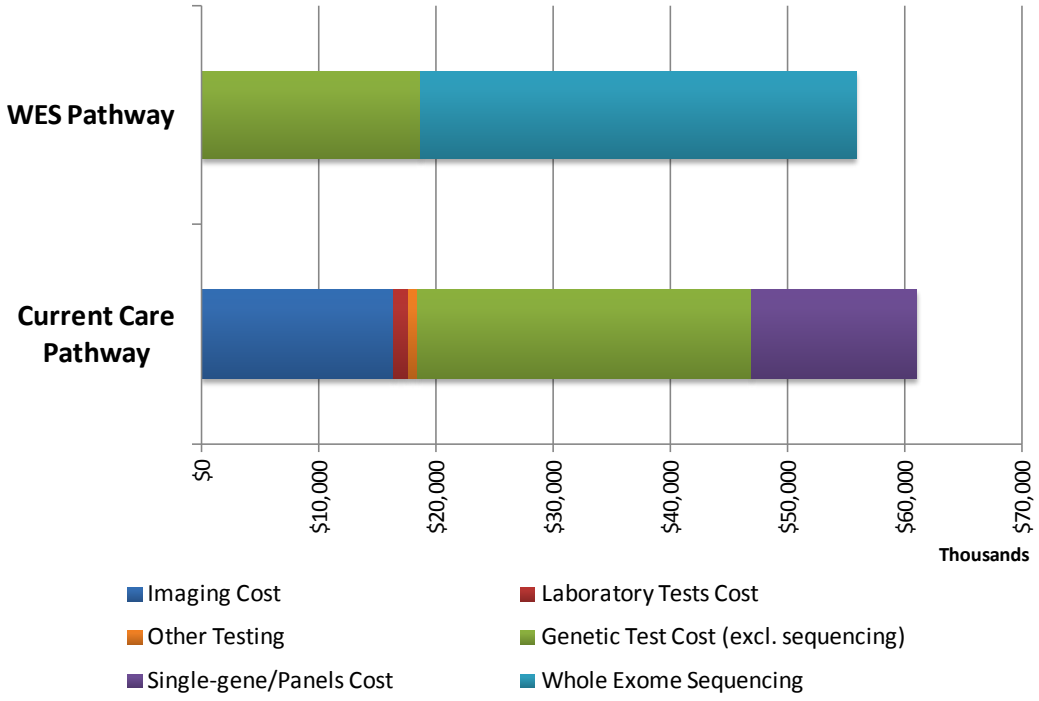


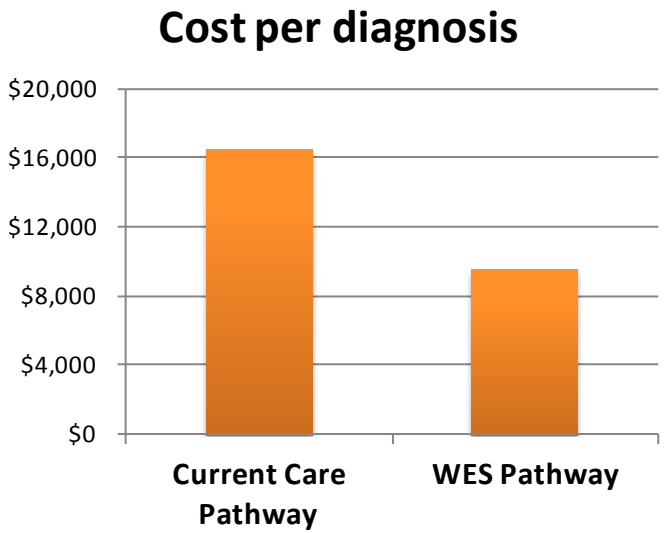
Key inputs: Exome

Variable	Model Input	Sources
Plan Demographics		
Number of Covered Lives	1 million	Representative plan size
Percent of members that are children with neuro-developmental disorders	1.239%	Census/CDC
Number of children with NDD in plan	12,394	Calculations
Standard of Care		
Percent of patients getting CT/MRI	95%	Patient data provided by KOL
Percent of patients getting ECG	29%	Patient data provided by KOL
Percent of patients getting EEG	76%	Patient data provided by KOL
Percent of patients getting ECG	53%	Patient data provided by KOL
Percent of patients getting Biopsies	34%	Data from Academic Medical Center
Percent of patients getting single-gene tests/gene panels	57%	Data from Academic Medical Center. Recommended in child born with hearing loss of any severity
Percent of patients getting Chromosomal microarray (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 WES	$3,000	Assumption (Model input)
Incremental diagnostic Yield of WES	30%	Srivastwa, Annual of Neurology 2014

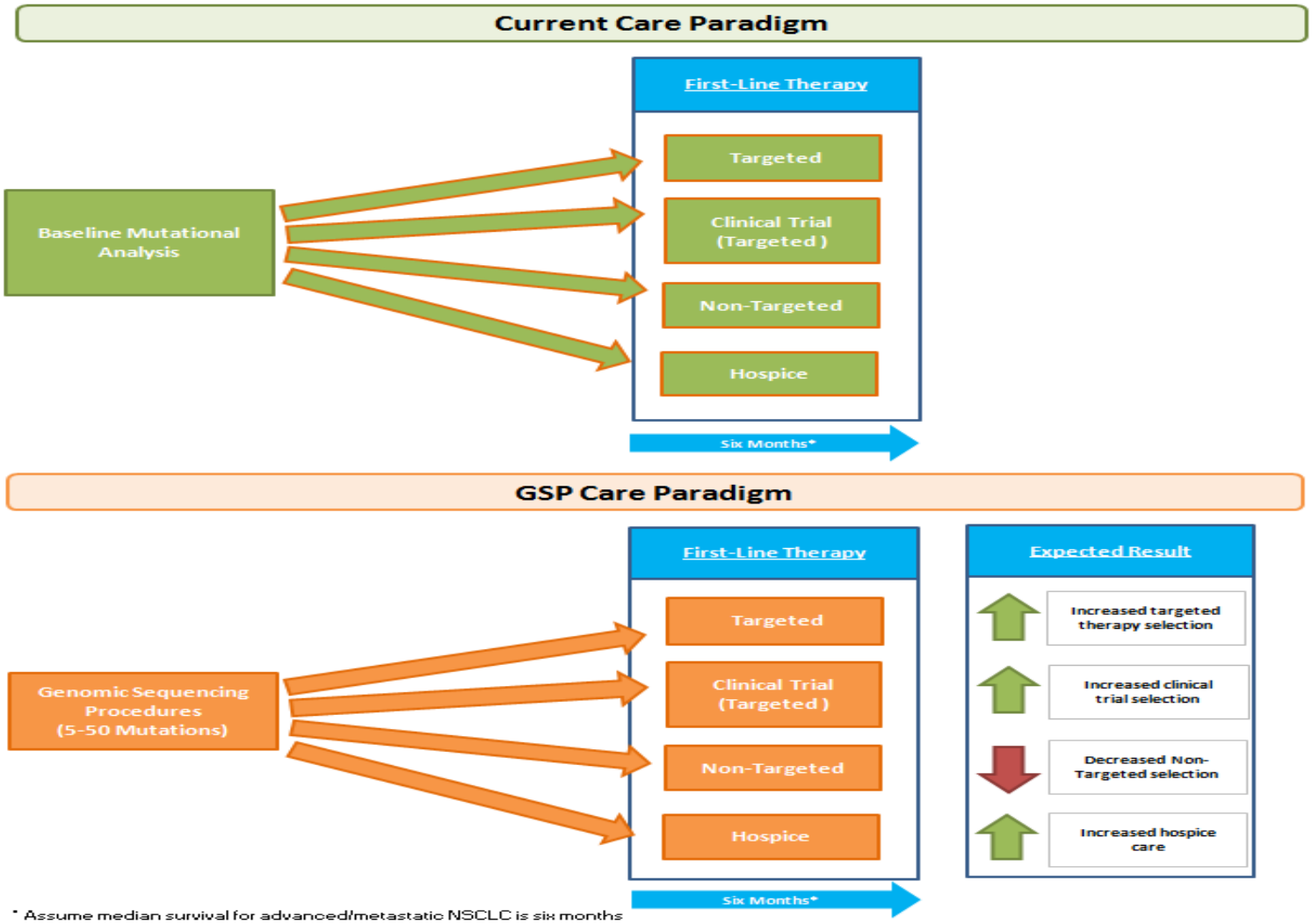
Results Summary: Exome

	Overall 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

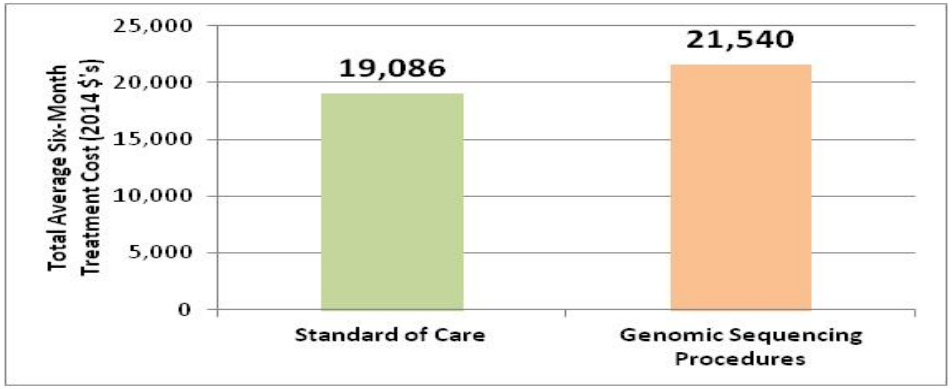


Key Inputs: NSCLC

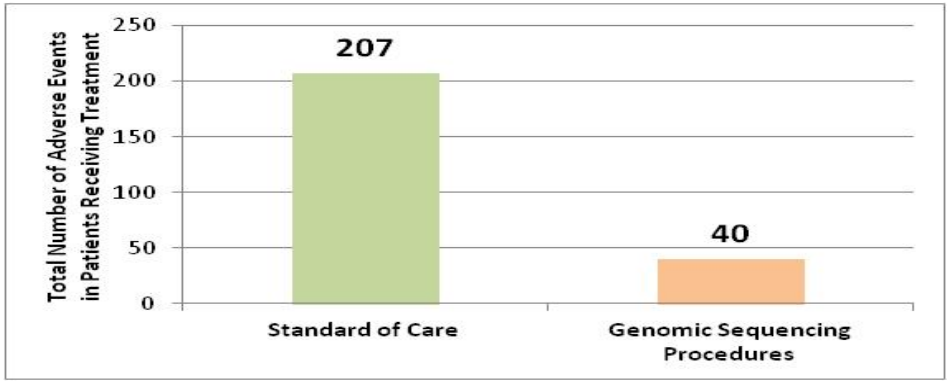
Variable	Model Input	Sources
Plan Demographics		
# of covered Lives	10 million	Representative plan size
Lung cancer incidence	.07%	Calculated based on total U.S. Population (U.S. Census Bureau) and annual lung cancer incidence rate (NCI SEER Stat Fact Sheet 2014)
Percentage of lung cancers diagnoses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

Result Summary: NSCLC

Total Average Treatment Cost

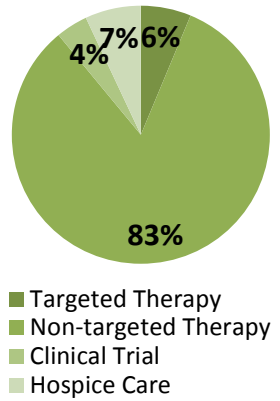


Total Number of Adverse Events

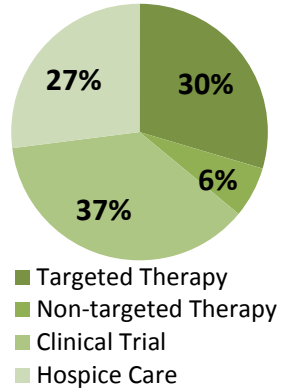


Treatment Decisions

Standard of Care



Genomic Sequencing Procedures



Putting These Tools into Practice

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Current Models

- The models represent a snapshot of current GSP procedures.
- Over time, these models should be adapted to reflect changes/innovations (e.g., platform/bioinformatics developments, introduction of FDA approved kits, and additional data (e.g., ASCO abstracts/publications on clinical utility of tumor panels).
- Also, these tools have not covered all potential current applications.

Template Model Overview

- To improve the sustainability and adaptability of these tools, we created a template micro-costing model.
- The template is:
  - A blank, detailed micro-cost model including structure and potential cost inputs and instructions for completion
  - A useful tool for labs who want to complete their own micro-cost models
- With the template, labs can use these cost modeling techniques and apply them to other current and future GSP application areas.

Template Model Has Built in Structure and Inputs for Completing Additional Micro-Cost Models

	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
			$ 0.00	0.00330
			$ 0.00	0.00330
87360	50%	2620800	$ 6,871.07	0.00262
87360	50%	2620800	$ 16,552.00	0.00632

SL105	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

Further Recommendations for Labs Performing GSPs

- Near term, AMP asks that labs use these models to articulate the cost and value of the GSP work they are doing to both Medicare and commercial payers.
- Longer term, labs should identify specific applications of GSPs, which can substantially impact clinical care in a cost-effective way.
- Collaborate with clinicians to create evidence which shows the clinical and economic value of GSPs.
  - Not just analytic validity/accuracy but also clinical utility relative to an often less than perfect current care paradigm
- Hone and articulate a value message that moves beyond cost of analytics into value of applications.
  - Including the value of assay development and bioinformatics /analytics

Thank You

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Committee Members

GSP Pricing Project Oversight Committee:

- Linda Sabatini, PhD, Sub-committee Chair (EAC)
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- Vivianna Van Deerlin, MD, PhD (AMP Board)
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- Ester Stein (EAC)
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If you are interested in assisting AMP's efforts through sponsorship, contact Mary Williams (mwilliams@amp.org).