Variants and Value

Marc S. Williams, MD
Director, Intermountain Healthcare
Clinical Genetics Institute
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Objectives

- Beyond clinical utility to value
  - Theoretical construct
- Application of construct to selected variants
- General comments on results of pre-conference inquiry
- Discussion

Actionablility vs. Clinical Utility

- Actionability
  - Knowledge of a variant implies a specific action for a given clinical scenario
- Clinical Utility
  - "… refers to the ability of a screening or diagnostic test to prevent or ameliorate adverse health outcomes such as mortality, morbidity, or disability through the adoption of efficacious treatments conditioned on test results"
  - "…any use of test results to inform clinical decision-making."

Grosse S, Khoury M. What is the clinical utility of genetic testing? Genet Med 8:448, 2006

Clinical Utility

- What are the components of usefulness, benefits, and drawbacks?
- How might we define and measure these factors?
- How should they be weighed against one another?
- Usefulness and relative benefit for whom?

Smart A. A multi-dimensional model of clinical utility. Int J Qual Health Care. 2006

Clinical Utility

Table 2 Summary of the dimensions of clinical utility

Component	Aspects	Issues that might be considered
Appropriate	Effective	Existence of formal evidence
	Relevant	Impact on existing treatment process
		Disruptions to current work or care
		Importance for clinical decision-making
Accessible	Resource implications	Costs and cost-effectiveness
	Procurement	Availability, supply, and quality
		Navigating finance processes (e.g. budgets, commissioning, and internal accounting)
Practicable	Functional	Are the materials, methods, or instructions complete and working?
	Suitable	Do the materials, methods, or instructions perform their tasks *in situ*?
	Training or knowledge	Adequacy of current levels and potential future needs
		Need to re-negotiate professional or work-practice boundaries
		Everyday constraints on training
Acceptable	To clinician	Ethical, legal, social, or psychological concerns that may affect practice
	To clients (including families and/or carers)	Ethical, legal, social, or psychological concerns that may affect treatment process
		Preferences about service delivery
	To society (public or stakeholder groups)	Ethical, legal, social, or psychological concerns that may affect acceptance

Smart A. A multi-dimensional model of clinical utility. Int J Qual Health Care. 2006

Clinical Utility Decision Factor Matrix

	Regulation	Coverage	Guidelines	QI	Individual Decisions
Efficacy					
Safety					
Effectiveness					
Comp. Effect.					
Cost/ CE					
Clinical Sit					
Legal/ Ethical					
Values/ Prefs					
Admin.					
Feasibility					
Stakeholders					

Courtesy Steven Teutsch

Value made simple?

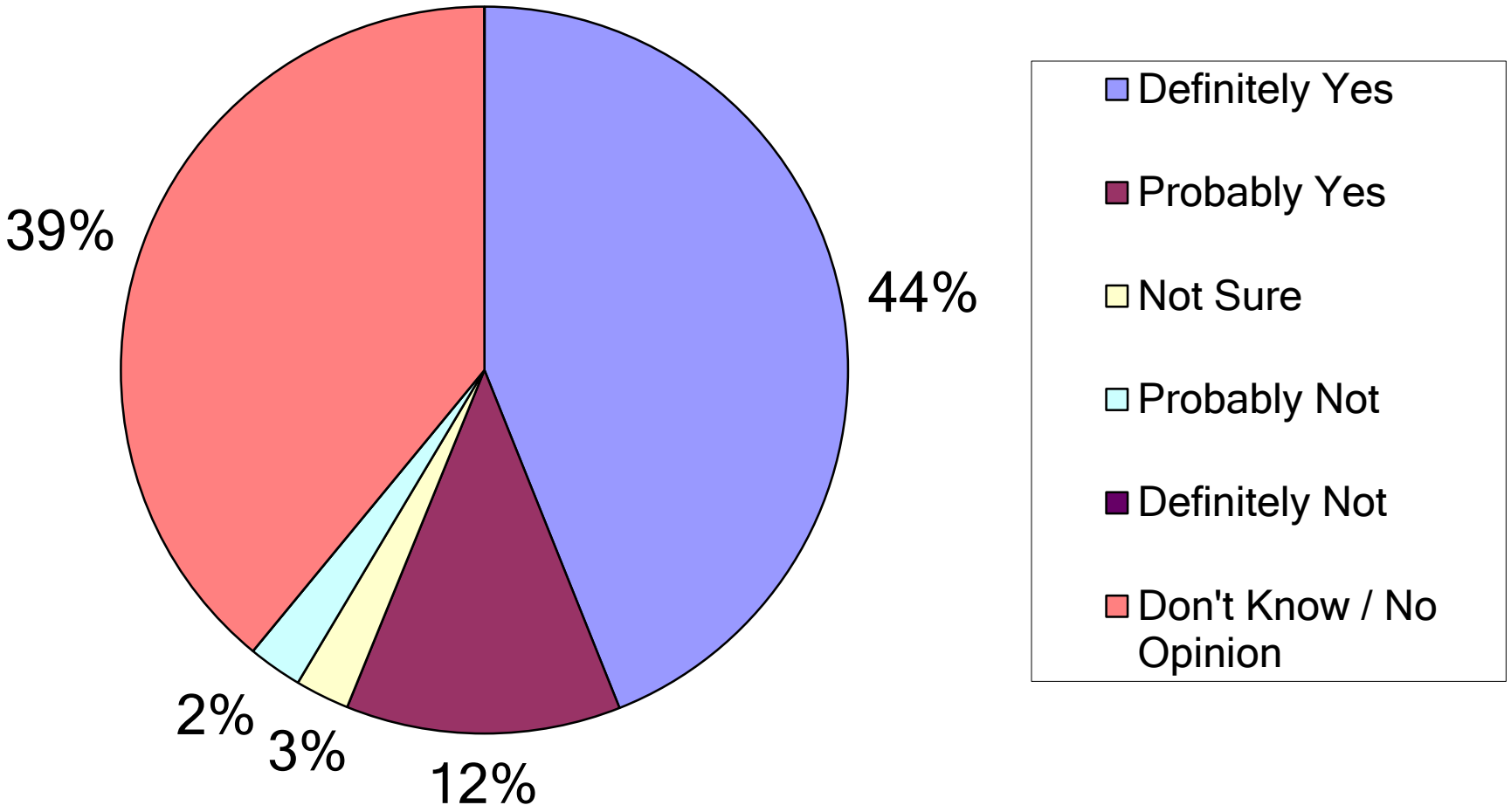
Value = Outcomes/Cost

Value made simple?

Cost of Care

Outcomes of Care	Decreased	Neutral	Increased
Improved	Yes	Yes	Maybe
Unchanged	Yes	Probably No	Definitely No
Worsened	Probably No	Definitely No	Definitely No

Scenario 1 - Variant to consider: **HLA-B*5701** Clinical situation: 28 year old man with HIV/AIDS to be started on Abacavir. Should this variant be routinely used in this clinical scenario?



N = 41

Scenario 1 - Variant to consider: **HLA-B*5701** Clinical situation: 28 year old man with HIV/AIDS to be started on Abacavir. Rank the following in order of importance as it relates to your answer with 1 being most important and 7 being least important.

Answer Options	1			4			7	N/A	Rating Average
Prevention of adverse event	**91%**	4%	0%	0%	4%	0%	0%	0%	1.22
Impact on efficacy of intervention	9%	13%	13%	4%	4%	17%	13%	**26%**	4.18
Impact on cost of care	0%	13%	13%	**26%**	17%	17%	4%	9%	4.29
Informs more precise dosing	9%	4%	4%	0%	4%	9%	26%	**44%**	5.08
Informs changes in patient care	**48%**	17%	17%	9%	4%	4%	0%	0%	2.17
Availability of published evidence	**44%**	26%	9%	9%	13%	0%	0%	0%	2.22
Professional society guideline/Regulatory agency statement (e.g. FDA Black Box warning)	13%	17%	**22%**	13%	13%	4%	9%	9%	3.48

Other factors that influenced your answer: Patient interest - i.e., informed patient that wants to know

N = 23

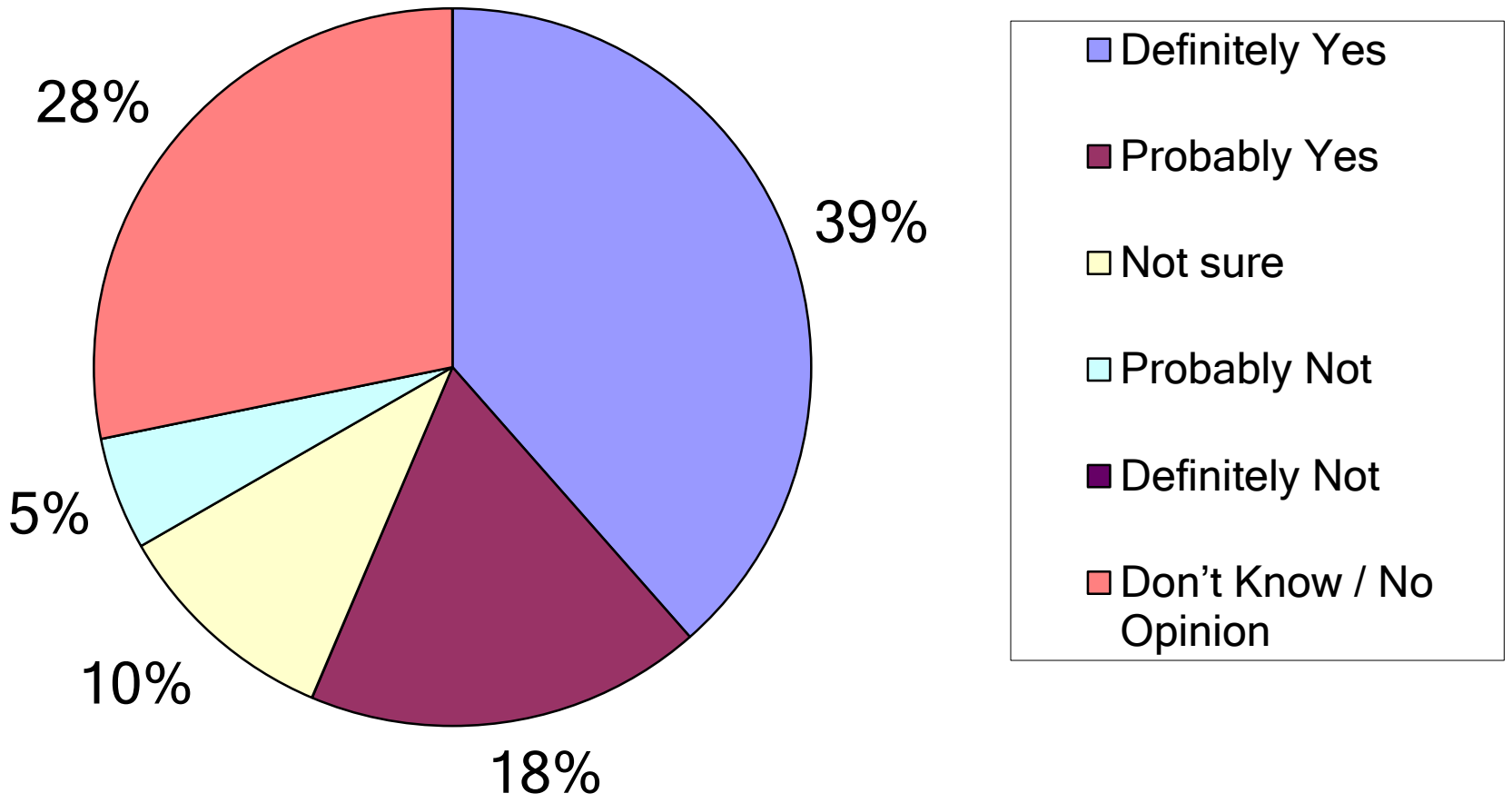
Value made simple-Abacavir Scenario

Cost of Care

Outcomes of Care	Decreased	Neutral	Increased
Improved	Yes **X**	Yes	Maybe
Unchanged	Yes	Probably No	Definitely No
Worsened	Probably No	Definitely No	Definitely No

How can we insure all patients prescribed Abacavir are tested?

Scenario 2 - Variant to consider: **TPMT*2 heterozygote** Clinical situation: Four year old girl with acute lymphoblastic leukemia being considered for treatment with 6-mercaptopurine. Should this variant be routinely used in this clinical scenario?



N = 39

Scenario 2 - Variant to consider: **TPMT*2 heterozygote** Clinical situation: Four year old girl with acute lymphoblastic leukemia being considered for treatment with 6-mercaptopurine. Rank the following in order of importance as it relates to your answer with 1 being most important and 7 being least important.

Answer Options	1			4			7	N/A	Rating Average
Prevention of adverse event	**58%**	15%	4%	0%	4%	4%	8%	8%	2.13
Impact on efficacy of intervention	**31%**	19%	4%	23%	12%	0%	0%	12%	2.61
Impact on cost of care	4%	15%	4%	15%	12%	19%	**23%**	8%	4.79
Informs more precise dosing	**39%**	27%	15%	4%	4%	4%	4%	4%	2.32
Informs changes in patient care	19%	**39%**	15%	12%	8%	4%	4%	0%	2.77
Availability of published evidence	**31%**	**31%**	8%	4%	15%	8%	0%	4%	2.64
Professional society guideline/Regulatory agency statement (e.g. FDA Black Box warning)	12%	**23%**	0%	8%	8%	**23%**	15%	12%	4.22

N = 26

Value made simple-*TPMT* Scenario 1

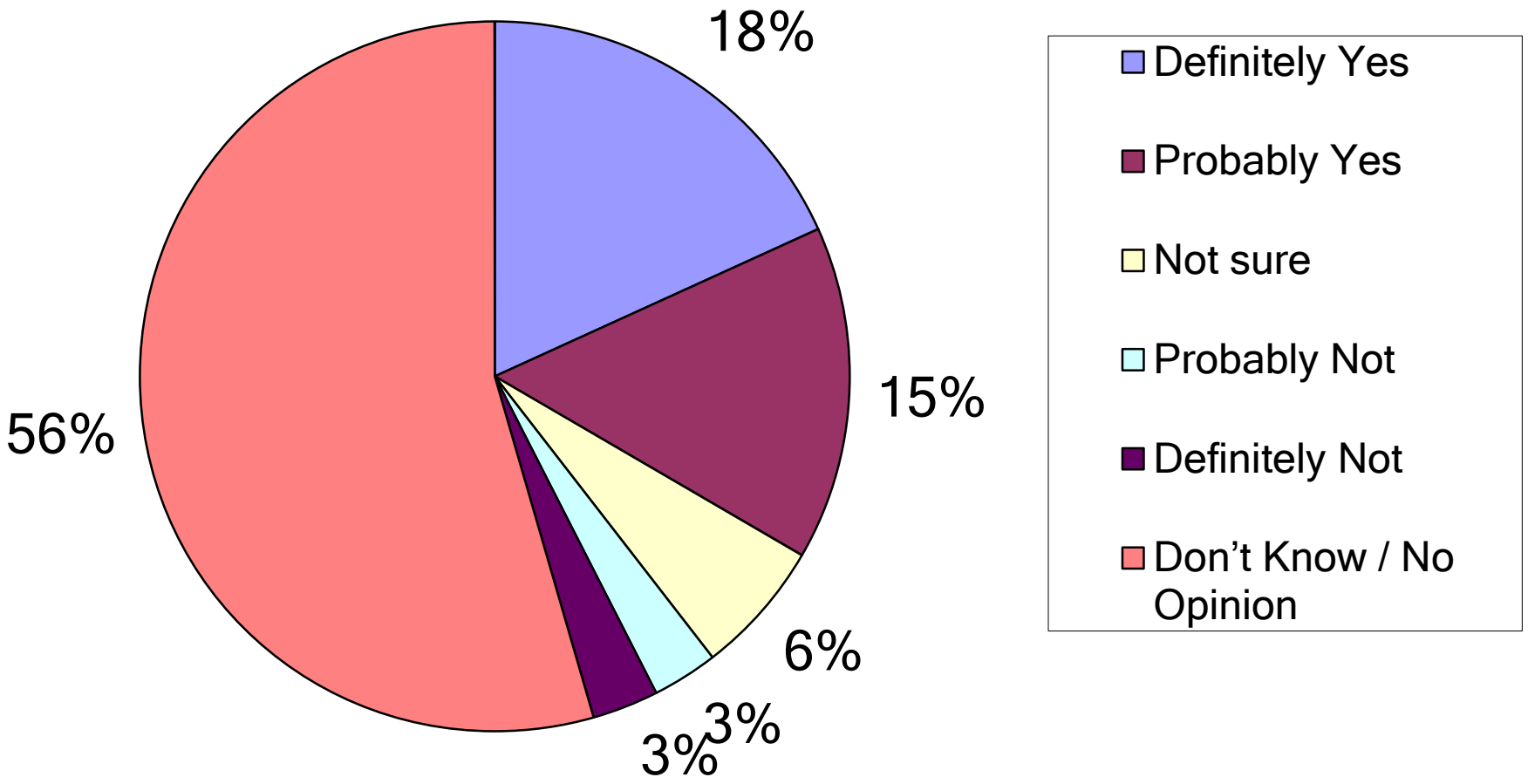
Cost of Care

Outcomes of Care	Decreased	Neutral	Increased
Improved	Yes **X***	Yes	Maybe
Unchanged	Yes	Probably No	Definitely No
Worsened	Probably No	Definitely No	Definitely No

*If only prevention of adverse events considered

How can we make sure evidence for both efficacy and adverse event prevention are considered for scenarios such as this?

Scenario 5 - Variant to consider: **TPMT*2 heterozygote** Clinical situation: 37 year old woman with inflammatory bowel disease being considered for treatment with 6-mercaptopurine. Should this variant be routinely used in this clinical scenario?



N = 33

Scenario 5 - Variant to consider: **TPMT*2 heterozygote** Clinical situation: 37 year old woman with inflammatory bowel disease being considered for treatment with 6-mercaptopurine. Rank the following in order of importance as it relates to your answer with 1 being most important and 7 being least important.

Answer Options	1			4			7	N/A	Rating Average
Prevention of adverse event	**67%**	20%	7%	7%	0%	0%	0%	0%	1.53
Impact on efficacy of intervention	**27%**	7%	13%	**27%**	7%	7%	7%	7%	3.29
Impact on cost of care	0%	7%	7%	**27%**	20%	7%	**27%**	7%	5.00
Informs more precise dosing	13%	13%	**33%**	0%	20%	7%	7%	7%	3.50
Informs changes in patient care	7%	**40%**	**40%**	7%	0%	7%	0%	0%	2.73
Availability of published evidence	**33%**	7%	7%	20%	20%	13%	0%	0%	3.27
Professional society guideline/Regulatory agency statement (e.g. FDA Black Box warning)	7%	7%	13%	7%	13%	**20%**	**20%**	13%	4.77

N = 15

Scenario 5 Continued - Variant to consider: **TPMT*2 heterozygote**
Clinical situation: 37 year old woman with inflammatory bowel disease being considered for treatment with 6-mercaptopurine. Rank the following in order of importance as it relates to your answer with 1 being most important and 7 being least important.

Other factors that influenced your answer:

•Level of evidence is fair to poor, no professional society guideline that I know of, need more evidence.

•Implications of testing still uncertain.

Value made simple-*TPMT* Scenario 2

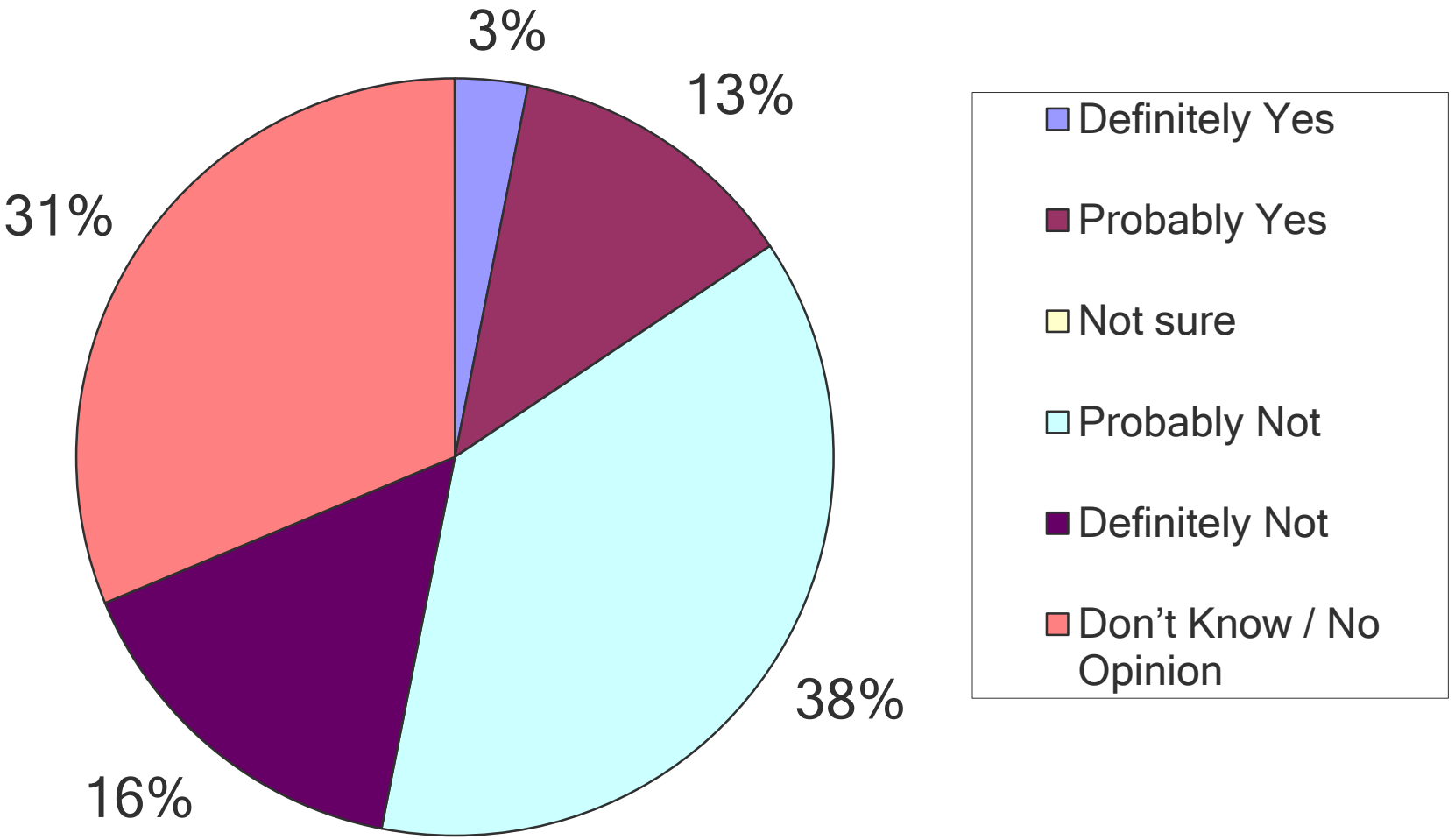
Cost of Care

Outcomes of Care	Decreased	Neutral	Increased
Improved	Yes **X***	Yes	Maybe
Unchanged	Yes	Probably No	Definitely No
Worsened	Probably No	Definitely No	Definitely No

*If only prevention of adverse events considered

How do we account for contextual differences for use of the same variant?

Scenario 10 - Variant to consider: **CYP450 profile** Clinical situation: 43 year old Caucasian woman with depression being considered for an SSRI. Should this variant be routinely used in this clinical scenario?



N = 32

Scenario 10 - Variant to consider: **CYP450 profile** Clinical situation: 43 year old Caucasian woman with depression being considered for an SSRI. Rank the following in order of importance as it relates to your answer with 1 being most important and 7 being least important.

Answer Options	1			4			7	N/A	Rating Average
Prevention of adverse event	9%	9%	0%	0%	**27%**	5%	23%	**27%**	4.81
Impact on efficacy of intervention	**18%**	**18%**	14%	14%	9%	9%	5%	14%	3.26
Impact on cost of care	5%	14%	14%	5%	9%	**18%**	**18%**	**18%**	4.56
Informs more precise dosing	5%	**23%**	0%	18%	14%	14%	5%	**23%**	3.94
Informs changes in patient care	14%	14%	9%	**27%**	9%	9%	5%	14%	3.58
Availability of published evidence	**41%**	23%	14%	0%	5%	14%	5%	0%	2.64
Professional society guideline/Regulatory agency statement (e.g. FDA Black Box warning)	14%	14%	5%	14%	0%	14%	14%	**27%**	3.94

N = 22

Scenario 10 Continued - Variant to consider: **CYP450 profile** Clinical situation: 43 year old Caucasian woman with depression being considered for an SSRI. Rank the following in order of importance as it relates to your answer with 1 being most important and 7 being least important.

Other factors that influenced your answer:

- Currently insufficient evidence for using PGx data to guide SSRI selection. One could make use of known PGx data without testing by simply choosing a drug metabolized by a different enzyme if the 1st choice is ineffective or not well tolerated (similar idea for statins & CYP3A4).

- Clinical utility unclear and unproven.

- EGAPP

Value made simple-CYP 450 profile

Cost of Care

Outcomes of Care	Decreased	Neutral	Increased
Improved	Yes	Yes	Maybe
Unchanged	Yes	Probably No	Definitely No
Worsened	Probably No	Definitely No	Definitely No

Insufficient evidence per EGAPP

Value made simple-CYP 450 profile

Cost of Care

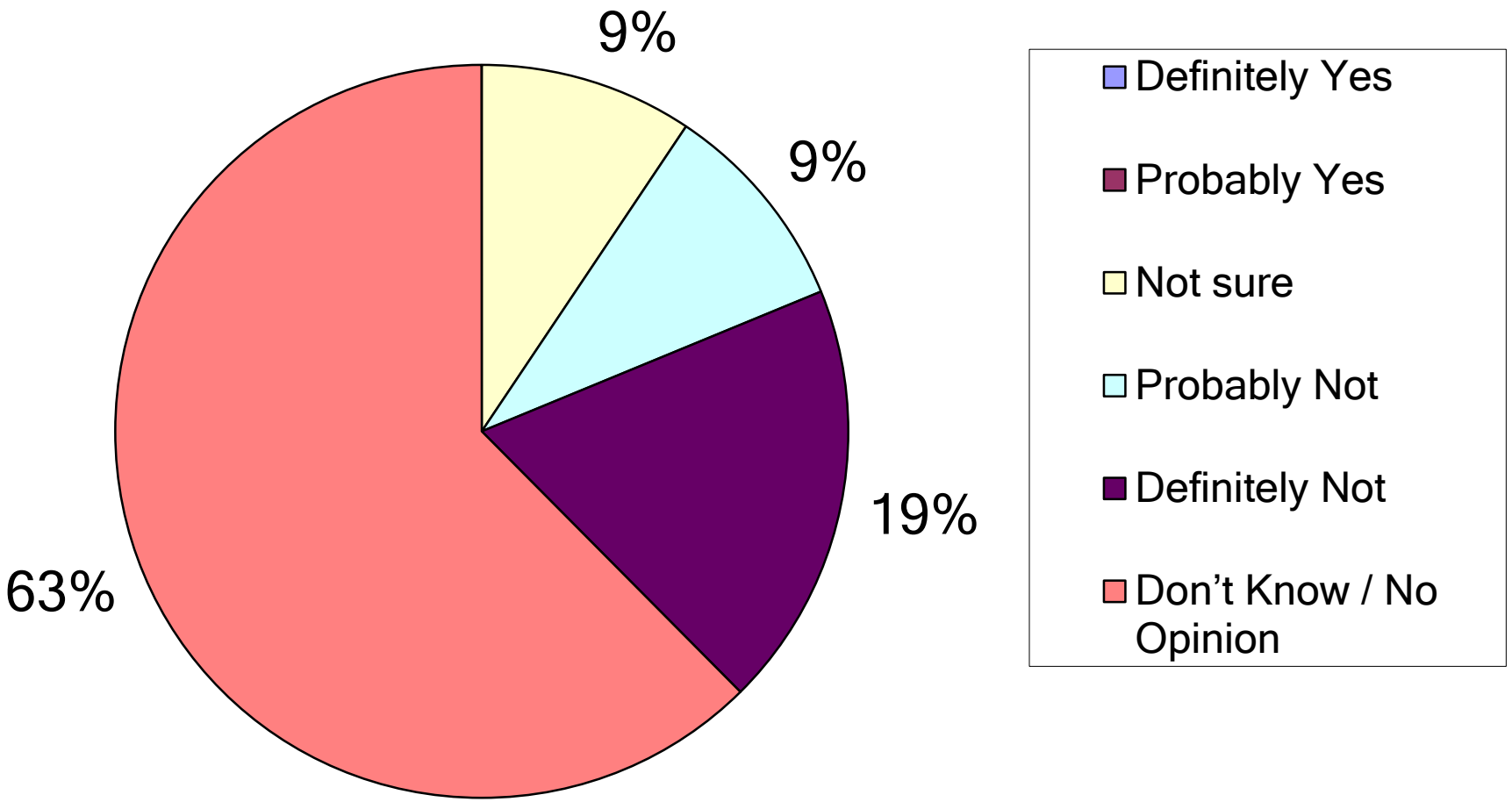
Outcomes of Care

	Decreased	Neutral	Increased
Improved	Yes **X***	Yes	Maybe
Unchanged	Yes	Probably No	Definitely No
Worsened	Probably No	Definitely No	Definitely No

*If believe Mrazek Mayo Clinic data

How do we rapidly translate clinical data into evidence for dissemination and implementation beyond initial system?

Scenario 8 - Variant to consider: **ScolioScore (multi-gene panel)** Clinical situation: Prediction of risk for curve progression in 12 year old girl with idiopathic scoliosis. Should this variant be routinely used in this clinical scenario?



N = 32

Scenario 8 - Variant to consider: **ScolioScore (multi-gene panel)** Clinical situation: Prediction of risk for curve progression in 12 year old girl with idiopathic scoliosis. Rank the following in order of importance as it relates to your answer with 1 being most important and 7 being least important.

Answer Options	1			4			7	N/A	Rating Average
Prevention of adverse event	8%	0%	17%	0%	0%	8%	0%	**67%**	3.25
Impact on efficacy of intervention	17%	17%	17%	8%	0%	8%	8%	**25%**	3.22
Impact on cost of care	8%	8%	8%	8%	8%	8%	8%	**42%**	4.00
Informs more precise dosing	0%	0%	0%	8%	0%	0%	8%	**83%**	5.50
Informs changes in patient care	17%	8%	17%	**33%**	0%	0%	0%	25%	2.89
Availability of published evidence	**42%**	17%	8%	8%	8%	0%	0%	17%	2.10
Professional society guideline/Regulatory agency statement (e.g. FDA Black Box warning)	0%	17%	0%	8%	0%	8%	8%	**58%**	4.20

N = 12

Scenario 8 Continued - Variant to consider: **ScolioScore (multi-gene panel)** Clinical situation: Prediction of risk for curve progression in 12 year old girl with idiopathic scoliosis. Rank the following in order of importance as it relates to your answer with 1 being most important and 7 being least important.

Other factors that influenced your answer:

- Hard to know whether 1 or 7 applies above, when there is lack of evidence and lack of published guideline. At any rate, this is a good example of the detrimental effects of the vacuum that exists with respect to LDTs and regulatory guidance. Also I think this test is available DTC, another gaping regulatory hole. Consumers get test, push for expensive interventions, limited evidence of clinical validity, lack of evidence for clinical utility, but consumer and doctor feel good about delivering the best medicine (it's personalized).

- No clinical utility.

Value made simple-Scolioscore scenario

Cost of Care

Outcomes of Care	Decreased	Neutral	Increased
Improved	Yes **X#**	Yes	Maybe
Unchanged	Yes	Probably No	Definitely No **X***
Worsened	Probably No	Definitely No	Definitely No

*Based on currently available evidence
#Based on product claims

How can the resource help clinicians to balance claims vs. evidence?

What variants are you currently using or evaluating for use in your clinical setting?

Answer	N	Answer	N	Answer	N
Clopidogrel PGx/CYP2C19	4	BRAF	1	HTR2A	1
Tamoxifen PGx/ CYP2D6	4	COMT	1	HTR2C	1
Warfarin PGx/CYP2C9 and VKORC1	4	CYP1A2	1	Pre-natal screening tests (CF etc.)	1
HLA-B*5701	2	DRD3	1	rs16969968	1
IL28B	2	DRD4	1	SLC6A4	1
KRAS	2	EGRF	1	TPMT	1
None	2	Exomes	1	Tumor variants	1
ALK/EML4	1	FLT3	1	UGT1A1	1
Any and all variants that are revealed in mainly adult clinical setting	1	FVL (rarely)	1	Variants in Mendelian disorders (e.g. cardiomyopathy, hearing loss/Usher/Pendred, Marfan, Noonan, APOL1, EDA, Paraganglioma, Lynch)	1
Autism CNVs	1	Germline	1		
BCR/ABL	1	HFE	1		

What resources or databases are you using to gather information about the variants in order to make the decision about clinical use?

Answer	N	Answer	N
Published literature/PubMed	12	1000 Genomes	1
Google/ Google Scholar	4	BlueCross BlueShield Technology Evaluation Center	1
PharmGKB	4	CYP nomenclature page	1
Clinical labs	2	Ensembl	1
dbSNP	2	GeneReviews	1
EGAPP	2	NCBI Variation Viewer	1
GeneTests	2	PGENI	1
HGMD	2	Signature Genomics Genoglyphix	1
LSDBs	2	UCSC Genome Browser	1
OMIM	2	U.S. Preventive Services Task Force	1

General Comments on Inquiry Results

- Large percentage of don't know/not sure responses
  - Some may be due to non-clinicians responding
  - Likely reflects current state of knowledge of most clinicians and public
- Extreme variability of opinion regarding most variants
- Demonstrates the need for the proposed resource!