The Role of Nursing in Precision Health Care

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Belinda Mandrell has no industry relationships to disclose

Precision Health Care Pharmacogenetics and Next Generation Sequencing Through the Lens of Pediatric Oncology


St. Jude Children's Research Hospital
Danny Thomas, Founder

Clinical Implementation of Pharmacogenetics PG4KIDS (2011)

- Genotyped for 230 pharmacogenes
- Committee determines results that are placed into medical record, as evidence supports clinical utility
- Results are updated according to evidence, each participant is given option to be notified of results
- June 2019, 9 pharmacogenes have been coupled to 35 drugs and are in medical record of participating patients

Cancer Predisposition

- It is estimated that 5-15% of children with cancer harbor an underlying predisposition

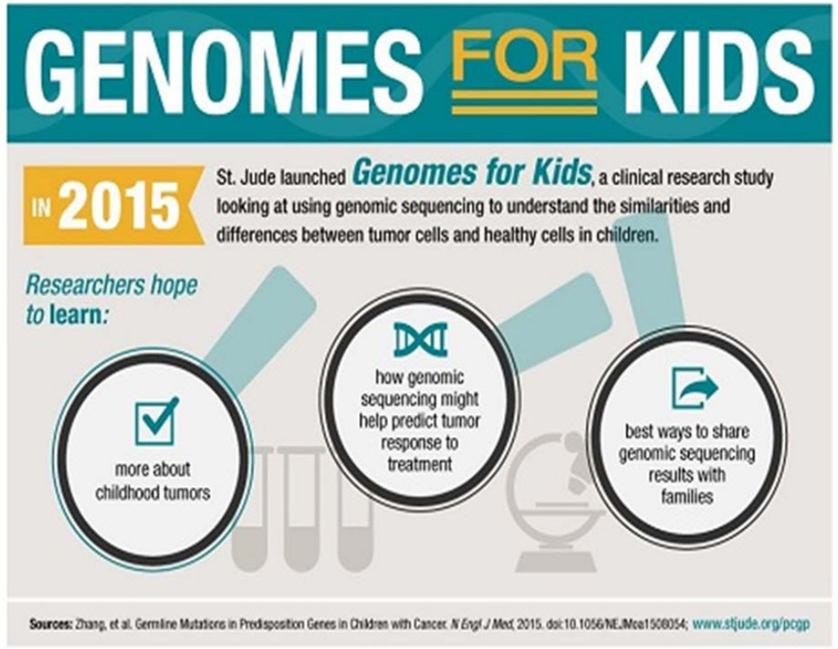
N Engl J Med. 2015 Dec 10;373(24):2336-2346. doi: 10.1056/NEJMoa1508054. Epub 2015 Nov 18.

Germline Mutations in Predisposition Genes in Pediatric Cancer.

Zhang J[#1], Walsh MF[#1], Wu G[#1], Edmonson MN[1], Gruber TA[1], Easton J[1], Hedges D[1], Ma X[1], Zhou X[1], Yergeau DA[1], Wilkinson MR[1], Vadodaria B[1], Chen X[1], McGee RB[1], Hines-Dowell S[1], Nuccio R[1], Quinn E[1], Shurtleff SA[1], Rusch M[1], Patel A[1], Becksfort JB[1], Wang S[1], Weaver MS[1], Ding L[1], Mardis ER[1], Wilson RK[1], Gajjar A[1], Ellison DW[1], Pappo AS[1], Pui CH[1], Nichols KE[#1], Downing JR[1].

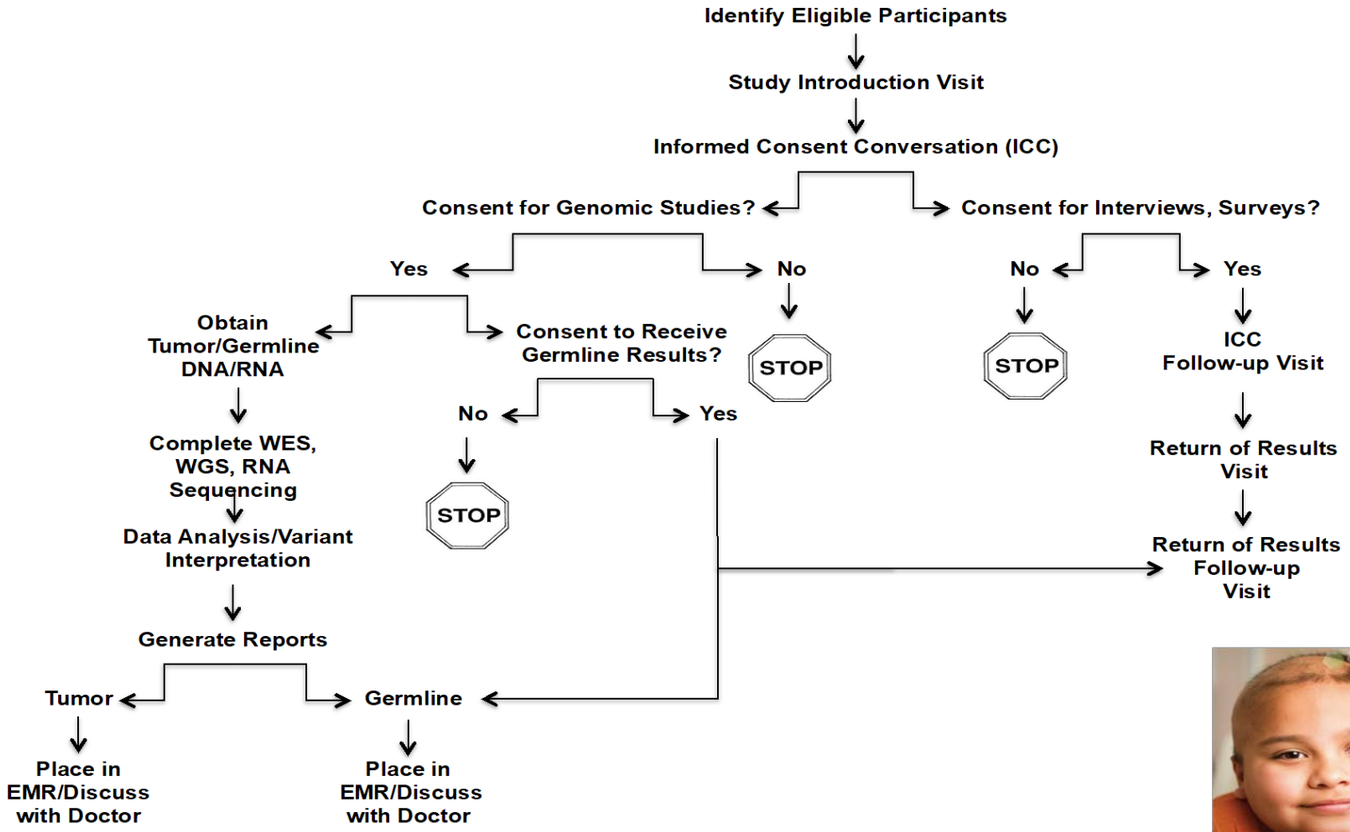
Next Generation Sequencing: G4K

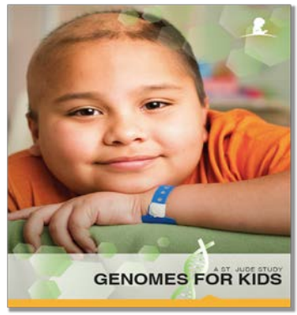
- Whole Genome Sequencing (WGS)
- Whole Exome Sequencing (WES)
- RNA Sequencing
- WGS and WES of paired germline sample



- **Impact of predictive Next Generation Sequencing on families**
- **What do parents and adolescents expect?**

Genomes for Kids





G4K Study Objectives

Primary Objectives	Exploratory Objectives
• To perform clinical next generation whole genome (WGS), exome (WES), and RNA sequencing on St. Jude pediatric oncology patients prospectively over a 24 month period	• To generate and analyze data describing the informed consent process and patient/parent perceptions of genomic investigations and research.
• To use WGS, WES and RNA sequence data to identify and characterize somatic genetic variants of pathological significance and germline genetic variants associated with increased cancer risk.	• To generate and analyze data describing the return of genomic sequencing results, examine patient/parent understanding of these results and assess the impact of results on patients and families.

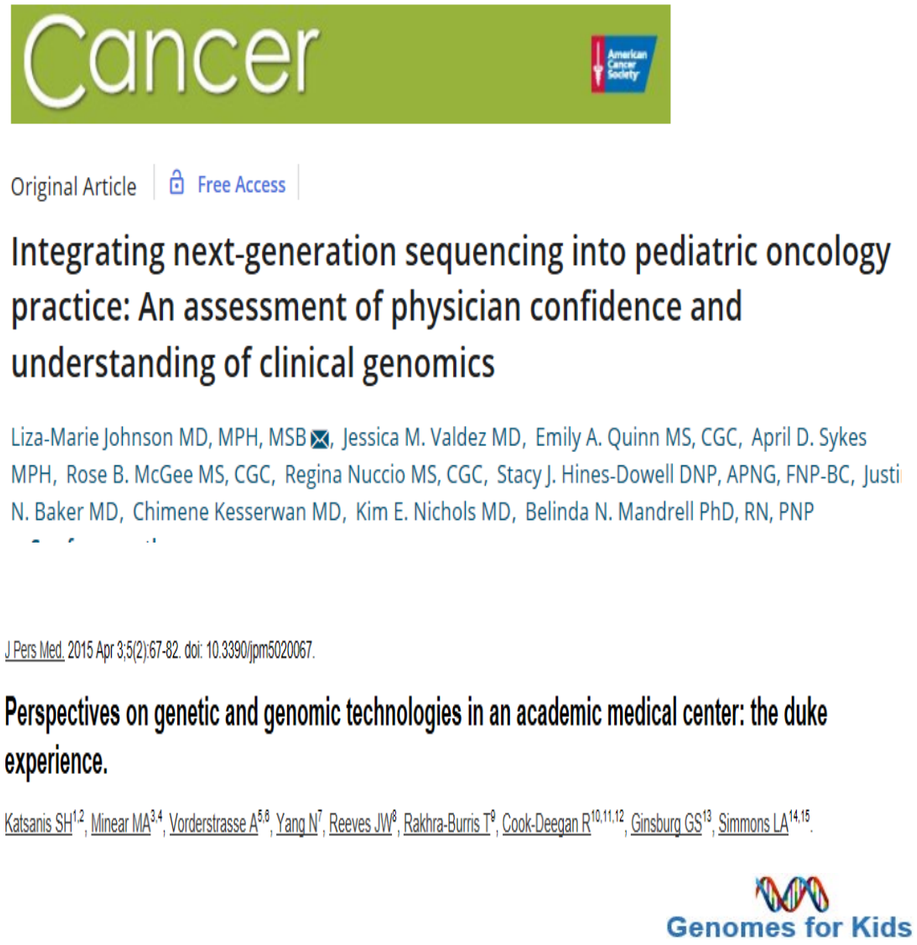
St. Jude Cloud In partnership with DNAnexus and Microsoft, St. Jude Children's Research Hospital has launched St. Jude Cloud, an online datasharing and collaboration platform that provides researchers access to the world's largest repository of pediatric cancer genomics data. Through this unique platform, St. Jude offers the world, free of charge, extensive next-generation sequencing data and unique analysis tools to accelerate research and cures for life-threatening pediatric diseases.

Considerations in Returning Results

- Provider confidence in discussing germline results is low

- Multiple studies report deficits in the perceived and actual knowledge of nurses, as well as their confidence in practice

(Calzone et al, 2012-2018)



Cancer

American Cancer Society

Original Article | Free Access

Integrating next-generation sequencing into pediatric oncology practice: An assessment of physician confidence and understanding of clinical genomics

Liza-Marie Johnson MD, MPH, MSB, Jessica M. Valdez MD, Emily A. Quinn MS, CGC, April D. Sykes MPH, Rose B. McGee MS, CGC, Regina Nuccio MS, CGC, Stacy J. Hines-Dowell DNP, APNG, FNP-BC, Justi N. Baker MD, Chimene Kesserwan MD, Kim E. Nichols MD, Belinda N. Mandrell PhD, RN, PNP

J Pers Med. 2015 Apr 3;5(2):67-82. doi: 10.3390/jpm5020067.

Perspectives on genetic and genomic technologies in an academic medical center: the duke experience.

Katsanis SH[1,2], Minear MA[3,4], Vorderstrasse A[5,6], Yang N[7], Reeves JW[8], Rakhra-Burris T[9], Cook-Deegan R[10,11,12], Ginsburg GS[13], Simmons LA[14,15].

Genomes for Kids

How Should Parents Receive Study Information in Making an Informed Consent

Two-Visit Informed Consent Model

- Parents of children with cancer were offered the opportunity to have their children's tumor and germline tissues studied using clinical genomic sequencing

- At the introductory visit:
  - Parents completed a baseline genetic knowledge
  - Parents completed self-reported literacy/numeracy

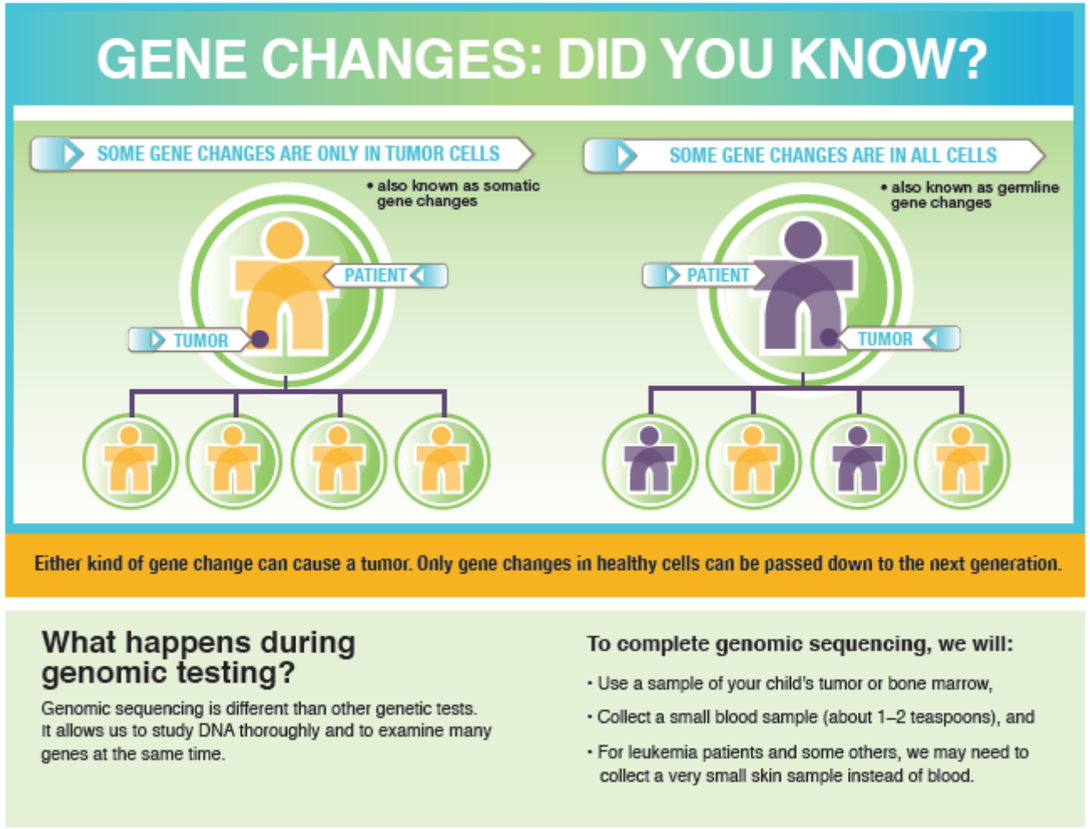
- Given basic concepts related to genomic sequencing

Two Visit Informed Consent Model:

Anastasia Ouma, MSN

- All education and consenting completed by one trained nurse
- Parents returned 1-3 weeks **after** introductory visit
- Information was re-enforced and informed consent obtained
- Post-test administered to reassess genetic knowledge

Structured Education



- **Study intro Visit**
- **Brochure**
- **Communication Checklist**
- **Script**

Survey Question	SIV	ICC	p=
1. Genes are made of DNA. ***True*** False I don't Know	 107 (91%) 4 (3%) 7 (6%)	 109 (92%) 7 (6%) (2%)	0.123
2. Genes are part of chromosomes. ***True*** False I don't Know	 96 (86%) 10 (8%) 13 (11%)	 109 (92%) 6 (5%) 4 (3%)	09.008*
3. Genes tell the cells of the body how to grow, develop and function. ***True*** False I don't Know	 94 (78%) 10 (8%) 16 (13%)	 118 (98%) 1 (1%) 1 (1%)	<0.0001*
4. Things in the environment may change how your genes work.* ***True*** False I don't Know	 34 (49%) 20 (29%) 15 (22%)	 50 (72%) 9 (1%) 10 (14%)	<0.001*
5. Genetic risk is the chance of having an inherited (passed down) disease or disorder. ***True*** False I don't Know	 118 (99%) 1 (1%)	 119 (100%) 0 (0%)	1.000
6. Healthy parents can have a child with an inherited disease. ***True*** False I don't Know	106 (89%) 3 (3%) 10 (8%)	115 (97%) 2 (2%) 2 (2%)	0.007*
7. If a parent has a gene mutation (change), the child will always have the same mutation. True ***False*** I don't Know	 0 0%) 98 (84%) 19 (16%)	 6 (5%) 105 (90%) 6 (5%)	0.003*
8. If a person inherits a gene mutation that is associated with developing cancer, it is certain that person will develop cancer. True ***False*** I don't Know	 1 (1%) 97 (81%) 22 (18%)	 7 (6%) 103 (86%) 10 (8%)	0.008*
9. Non-tumor (germline) mutations are in every cell of your body. ***True*** False I don't Know	 37 (31%) 22 (19%) 59 (50%)	 75 (64%) 22 (19%) 21 (18%)	<0.0001*
10. Tumor (somatic) mutations are only found in cancer cells. ***True*** False I don't Know	 21 (18%) 45 (38%) 51 (18%)	 69 (59%) 28 (24%) 20 (17%)	<0.0001*
11. Genomic testing of child may teach you things about: Genomic testing of your child's tumor and health tissue may teach you things about: [b] A = Diseases or conditions that might affect y our child B = Diseases or conditions that might affect other members of your family ***C = Both A and B***	 8 (7%) 3 (3%) 103 (90%)	 2 (2%) 0 (0%) 112 (98%)	0.018*

Findings : Two-Visit Consent Model

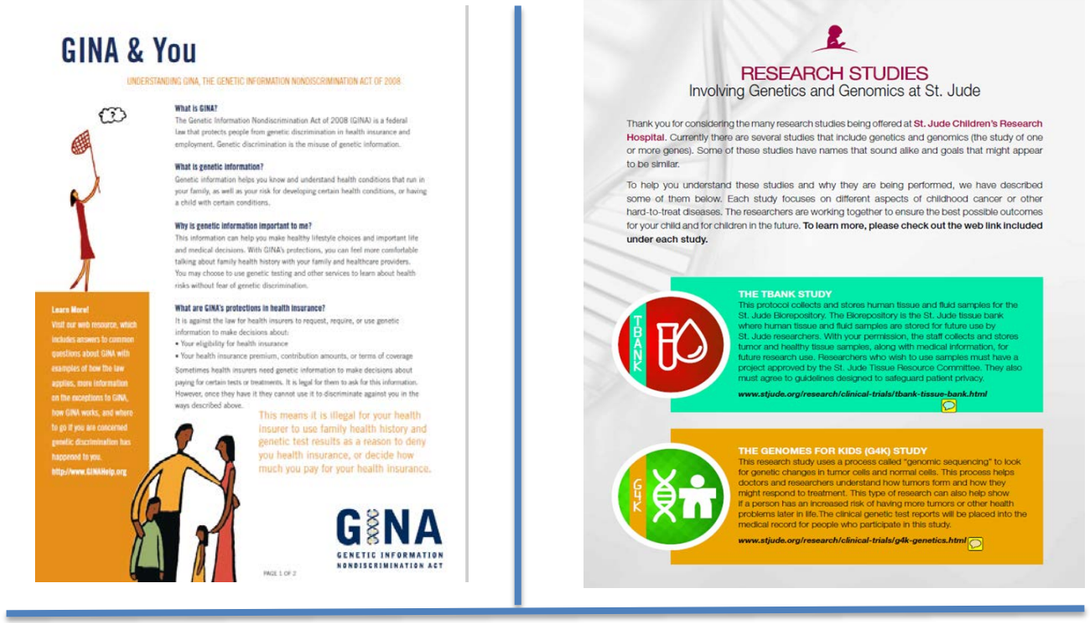
- Genomic knowledge increased by 11% (77.8 to 88.9%, p<0.0001)
- Understanding of somatic mutations improved (18 to 59%, p <0.0001)
- Understanding of germline mutations improved (31 to 64%, p <0.0001)
- The concept of somatic and germline mutations remained unfamiliar to approximately one-third of the parents

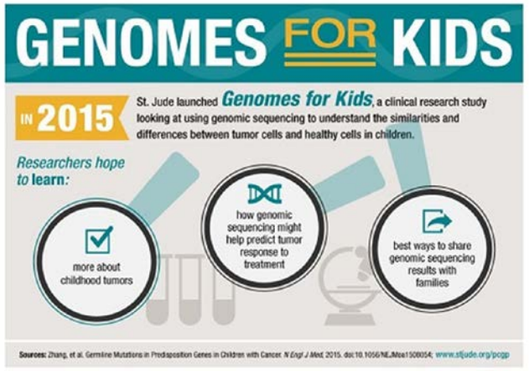
No Association between parent reported literacy and numeracy skills and the percent of correct answers on the genetic knowledge test

	Change in the overall percent of correct answers (ICC-SIV)[a]		
	N	Median (IQR)	P[b]
Literacy: How confident are you filling out forms by yourself			
Not at all/A little bit/Somewhat	29	11.11 (0 to 33.33)	0.720
Quite a bit/Extremely	91	11.11 (0 to 22.22	
Subjective Numeracy Scale (SN-3): How good are you at working with fractions			
1-3 (Low/Intermediate)	56	11.11 (0 to 27.78)	0.558
4-5 (High)	64	11.11 (0 to 22.22)	
How often do you find numerical information useful?			
1-3 (Low/Intermediate)	30	16.67 (0 to 22.22)	0.228
4-5 (High)	90	11.11 (0 to 22.22)	
How good are you at figuring out how much a shirt will cost if it is 35% off?			
1-3 (Low/Intermediate)	26	11.11 (0 to 22.22)	0.951
4-5 (High)	93	11.11 (0 to 22.22)	

Conclusion

- The two-visit model improved knowledge
- Somatic and germline mutations remain difficult concepts
- Ongoing discussion and reinforcement of unfamiliar concepts is needed to achieve adequate understanding





Cancer

Original Article | Full Access

Speaking genomics to parents offered germline testing for cancer predisposition: Use of a 2-visit consent model

Liza-Marie Johnson MD, April D. Sykes MPH, Zhaohua Lu PhD, Jessica M. Valdez MD, Jami Gattuso MSN, Elsie Gerhardt MA, Kayla V. Hamilton MS, Lynn W. Harrison MPA, Stacy J. Hines-Dowell DNP, Niki Jurbergs PhD, Rose B. McGee MS, Regina Nuccio MS, Annastasia A. Ouma RN, Michele Pritchard PhD, Emily A. Quinn MS, Justin N. Baker MD, Belinda N. Mandrell PhD, Kim E. Nichols MD

... See fewer authors

First published: 22 March 2019 | https://doi.org/10.1002/cncr.32071

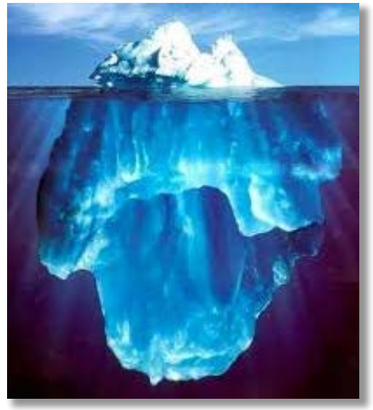
Results in 363 Patients with Cancer

- Patients presented with newly diagnosed disease, relapsed, refractory or secondary cancer
- Approximately 1000 cancer-related genes/pathways have been found to be mutated in the somatic sample
- 63 cancer predisposition genes then expanded to an additional 93 genes (156) known cancer genes are being evaluated in the germline sample
- Germline samples are presented as Positive (LP), VUS, Negative

Why Examine Genes from Both Cancer and Healthy Cells

- **Etiology** (n=11)
- Understanding of the concept of **Somatic versus Germline** (n=11)
- **Not grasp** the concept of why this comparison is being done (n=7)
- **Hereditary** (n=6)
- Other, less frequent codes—determine chance for **future relapse or new cancer**, to **target treatment** for the child's cancer

What is the Clinical Utility



- Understanding of clinical implications of genetic variants are still evolving
- Genotype – Phenotype Relationships
- Surveillance and Accountability

Conclusion: Returning research results within the context of large-scale genomics research is a labor-intensive, highly variable, complex operation. Results that warrant action are not infrequent, but the prevalence of those who experience a clinical difference as a result of returning individual results is currently low

Johns AL et al. “Lost in translation: returning germline genetic results in genome-scale cancer research. *Genome Medicine* 2017

Considerations in Returning Variant Results

- Debate exists around variant calling, what variants to return, and variant reanalysis.

ELSEVIER

European Journal of Medical Genetics

journal homepage: www.elsevier.com/locate/ejmg

Underdiagnoses resulting from variant misinterpretation: Time for systematic reanalysis of whole exome data?

Fathiya Al-Murshedi[a], Douja Meftah[a], Patrick Scott[b,*]

- Re-analysis may find variants with clinical significance.
  - *"~22% of individuals who did not receive a P/LP variant at their original analysis subsequently did after 3 years."* *(Hiatt et al, 2018)*

CLINICAL GENETICS An International Journal of Genetics, Molecular and Personalized Medicine

SHORT REPORT | Full Access

Systematic reanalysis of genomic data improves quality of variant interpretation

S.M. Hiatt, M.D. Amaral, K.M. Bowling, C.R. Finnila, M.L. Thompson, D.E. Gray, J.M.J. Lawlor, J.N. Cochran, E.M. Bebin, K.B. Brothers, K.M. East, W.V. Kelley, N.E. Lamb, S.E. Levy, E.J. Lose, M.B. Neu, C.A. Rich, S. Simmons, R.M. Myers, G.S. Barsh, G.M. Cooper

Family Preferences Around Return of Results

VOLUME 27 · NUMBER 6 · FEBRUARY 20 2009

JOURNAL OF CLINICAL ONCOLOGY

- Parents (94%) and adolescents (85%) feel a (very) strong right to receive research results

Providing Research Results to Participants: Attitudes and Needs of Adolescents and Parents of Children With Cancer

Conrad Vincent Fernandez, Jun Gao, Caron Strahlendorf, Albert Moghrabi, Rebecca Davis Pentz, Raymond Carlton Barfield, Justin Nathaniel Baker, Darcy Santor, Charles Weijer, and Eric Kodish

Element	Parents		Adolescents	
	No.	%	No.	%
Are there any long-term problems for participants?	341	83.4	45	52.3
Do I need to do anything for my future health because of the study?	290	70.9	48	55.8
Provide information that may improve quality of life	315	77.0	54	62.8
Provide information that may prevent future harms	259	63.3	51	59.3
No good reasons to return results	4	1.0	2	2.3

Survey Data

Parental Interest in Genomic Results (N = 131)

Would you want to know germline genomic results that may have health implications for your child who was tested?	Yes	128 (97.7%)
	Unsure	1 (0.8%)
	Did not answer	2 (1.5%)
Would you want to know germline genomic results that may have health implications for your other children?	Yes	107 (96.4%)
	No	3 (2.7%)
	Did not answer	1 (0.9%)
Would you want to know germline genomic results that may have health implications for you?	Yes	126 (96.2%)
	No	2 (1.5%)
	Unsure	3 (2.3%)
Would you want to know about your child's germline genomic results for a disease that has a treatment or is preventable?	Yes	131 (100%)
Would you want to know about your child's germline genomic results for a disease that has no treatment or is not preventable?	Yes	123 (93.9%)
	No	2 (1.5%)
	Unsure	6 (4.6%)

Adolescent Interest in Genomic Results (N = 30)

If you do want to learn your test results, which of the following could you like to know about? Select all that apply.		
Disease or health conditions that are very likely to happen	no	1 (3.4%)
	yes	28 (96.6%)
Disease or health conditions that could be prevented or treated in childhood	no	2 (6.7%)
	yes	28 (93.3%)
Disease or health conditions that could be prevented or treated in adulthood	no	3 (10%)
	yes	27 (90%)
Disease or health conditions that might affect me or my family members	yes	30 (100%)
Results where the impact on my future health is not known	no	3 (10.3%)
	yes	26 (89.7%)

Do you want to know genetic results that may affect your health or other family members' health, such as siblings or parents?	Yes	29 (96.7%)
	Unsure	1 (3.3%)
Would you want to know about genetic results for a disease that has a treatment and/or is preventable?	Yes	28 (93.3%)
	Unsure	2 (6.7%)
Would you want to know about genetic results for a disease that has no treatment and/or is not preventable?	Yes	21 (72.4%)
	Unsure	8 (27.6%)

Differences in Preferences around ROR

I believe parents have a right to know only the germline genetic results that are important to their child's health during childhood.

- The child can decide, when old enough, whether he or she wants to know about any results that are important in adulthood.

Choice	Father (n=56)	Mother (n=136)	P*
Yes	20 (60.6%)	32 (34%)	**0.034**
No	8 (24.2%)	40 (42.6%)	.
Unsure	5 (15.2%)	21 (22.3%)	.
Did not answer	0 (0%)	1 (1.1%)	.

I believe parents have a right to know all of the germline genetic results, irrespective of whether or not they are important during childhood or adulthood.

Choice	New patient, new cancer (n=109)	Relapsed/Refractory/ Second cancer (n=22)	P*
Yes	104 (95.4%)	18 (81.8%)	**0.013**
No	0 (0%)	2 (9.1%)	.
Unsure	5 (4.6%)	2 (9.1%)	.

Expectations for Updated Genomic Results

			Dyads		
Questions	**Parent (n=197)**	**Teenager (n=31)**	**Parent (n=28)**	**Teenager (n=28)**	**P (Bhapkar)**
Do researchers or your doctor have a responsibility to contact you/your child with new germline test results or changes to your child's germline test results?					0.185
Yes	**189 (95.9%)**	**26 (86.7%)**	27 (100.0%)	24 (88.89%)	
No	0 (0.0%)	1 (3.3%)	0 (0.00%)	1 (3.70%)	
Unsure	5 (2.5%)	3 (10%)	0 (0.00%)	2 (7.41%)	
Did not answer	3 (1.5%)				
If you answer YES, what is your opinion of how long researchers should follow up with study participants?					0.56
5-10 years after study participation	1 (0.6%)	1 (4.5%)	1 (5.26%)	0 (0%)	
As long as my child is coming for appointments, even as an adult	**51 (29.7%)**	**7 (31.8%)**	6 (31.58%)	6 (31.58%)	
At any time, or until I/my child ask you to stop	**120 (69.8%)**	**14 (63.6%)**	12 (63.16%)	13 (68.42%)	

Expectations for Updated Genomic Results

Questions	Parent (n=197)	Teenager (n=31)	Parent-Teen dyads		P (Bhapkar)	P (Kappa)
			Parent (n=28)	Teenager (n=28)		
If my child passed away, I would still want to be contacted with new information about the germline test results or changes to the germline test results.					0.595	0.309
Yes	**133 (67.5%)**	**24 (85.7%)**	18 (69.23%)	21 (80.77%)		
No	**21 (10.7%)**	0 (0.0%)	0 (0.00%)	0 (0.00%)		
Unsure	**38 (19.3%)**	**4 (14.3%)**	8 (30.77%)	5 (19.23%)		
Did not answer	5 (2.5%)					

- Parents and teens want to receive most germline results.
- Expectations for return of results are high & (likely) not limited by time from original testing.
- Many parents desire updated information after loss of a child, but nearly 1/3 are uncertain or have concerns.

Clear communication (prior to testing) that explains results to be returned and aligns expectations around the return (or non-return) of future genomic information!

What Is the Parents Emotional Reaction

- Identify patterns of parents' sequencing-related emotional reactions prior to the disclosure of Next-Generation Sequencing results
  - Sequencing-related worries
  - Guilt
  - Peace of mind
  - Hope
- Examine demographic and clinical predictors of parents' membership in these profiles

Method: Measures

- Modified Psychosocial Aspects of Hereditary Cancer Questionnaire (PAHC)

Psycho-Oncology
Psycho-Oncology **23**: 862–869 (2014)
Published online 20 January 2014 in Wiley Online Library (wileyonlinelibrary.com). **DOI**: 10.1002/pon.3485

Psychosocial Aspects of Hereditary Cancer (PAHC) questionnaire: development and testing of a screening questionnaire for use in clinical cancer genetics

W. Eijzenga, E. M. A. Bleiker, D. E. E. Hahn, I. Kluijt, G. N. Sidharta, C. Gundy and N. K. Aaronson*
Department of Psychosocial Research and Epidemiology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

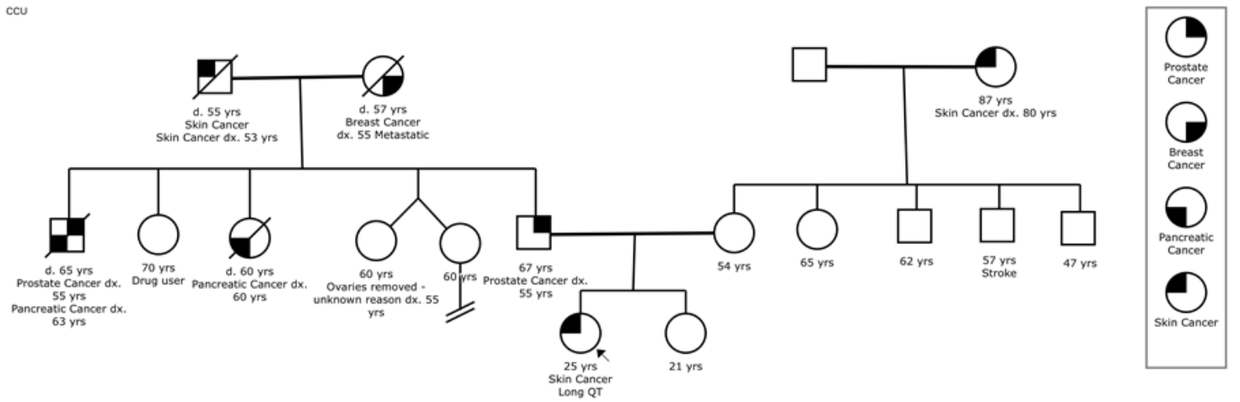
PAHC items

- ~~Do you feel misunderstood by your partner, family, or other people about this germline genomic testing?~~
- ~~Are you bothered by a lack of support for your germline genomic testing choice?~~

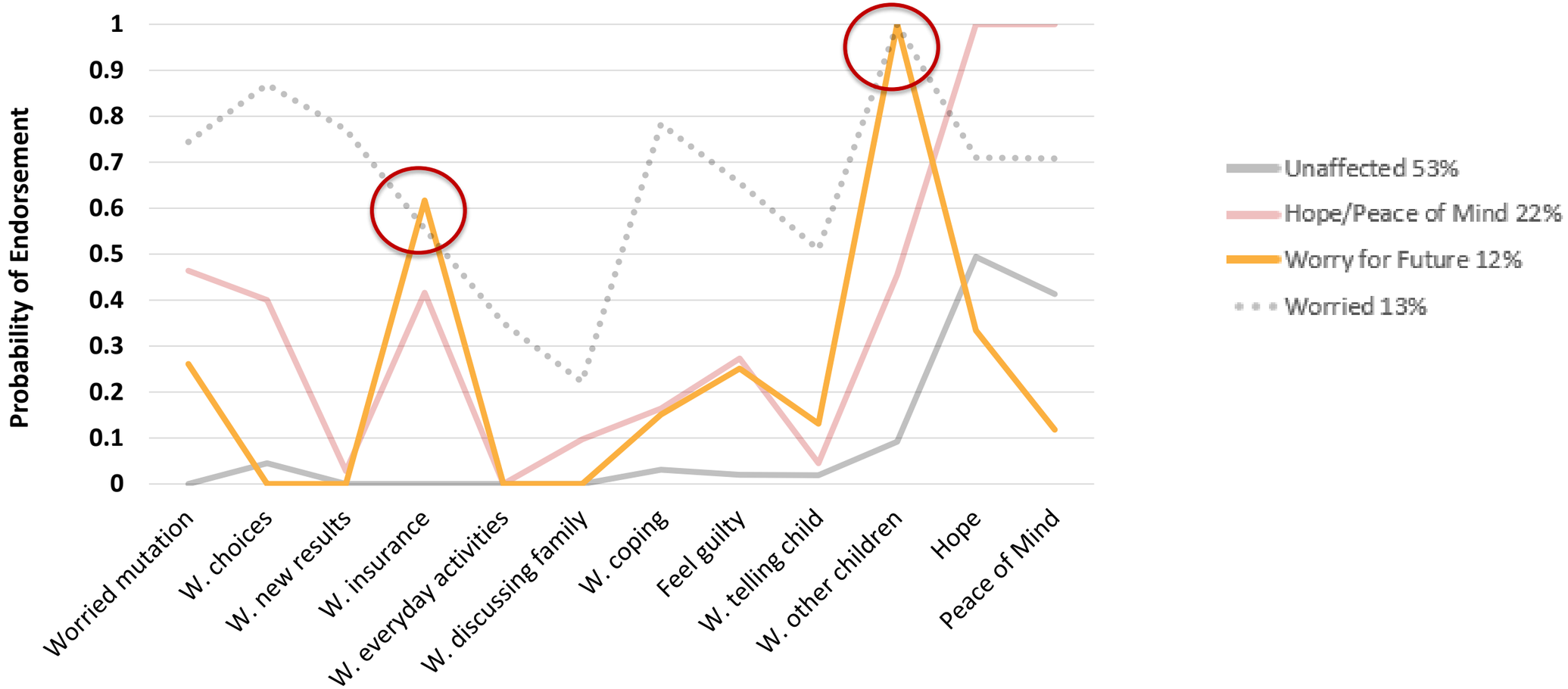
- **Do you feel that participation in this study has given you more hope for cure of your child's cancer?**
- **Do you feel that participation in this study has given you greater peace of mind?**

Method: Measures

- Demographic variables:
    - Ethnicity, race, sex, parent age, child age, income, martial status, education, religion
- Clinical Variables:
    - Time since consent, relapse, tumor type
    - Family history of cancer



Parent Psychological Reactions Pre-Disclosure



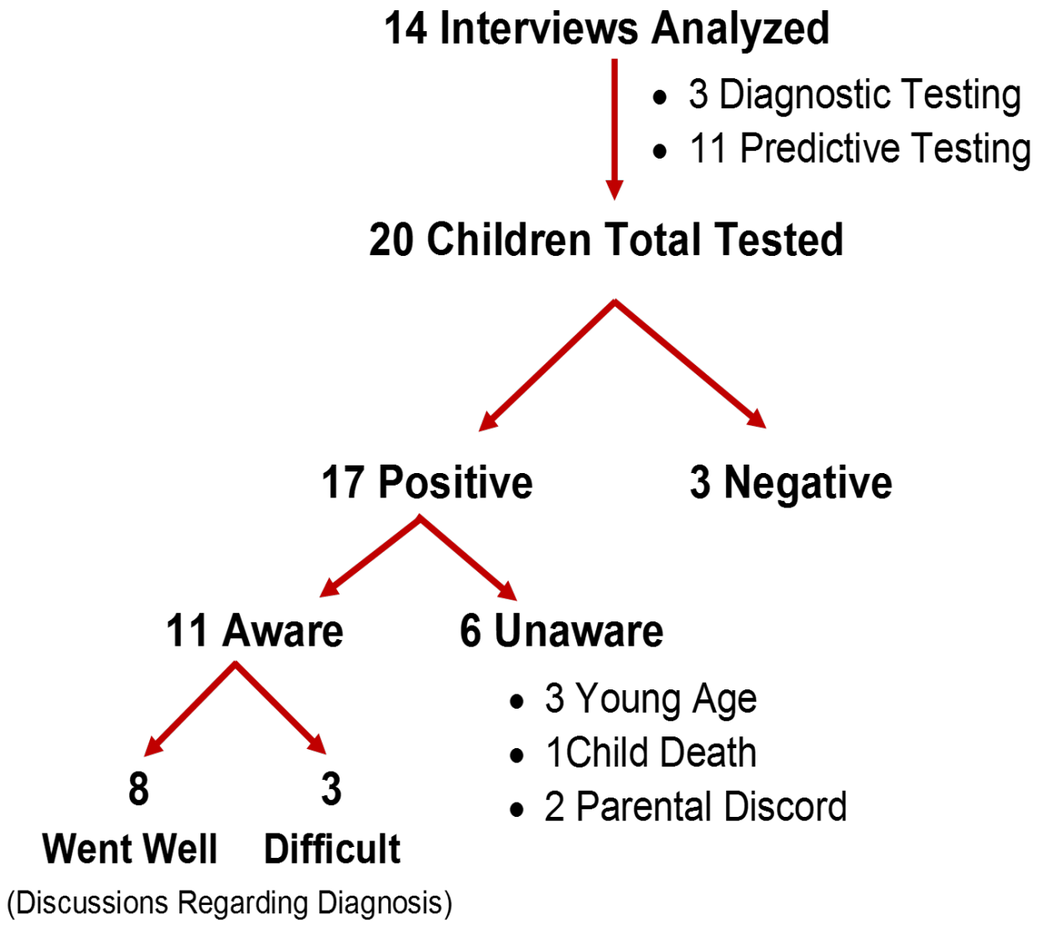
Summary

- Variables associated with risk for higher pre-disclosure worries
  - Family history of cancer
  - Less time since consent
  - Lower Education
  - Race

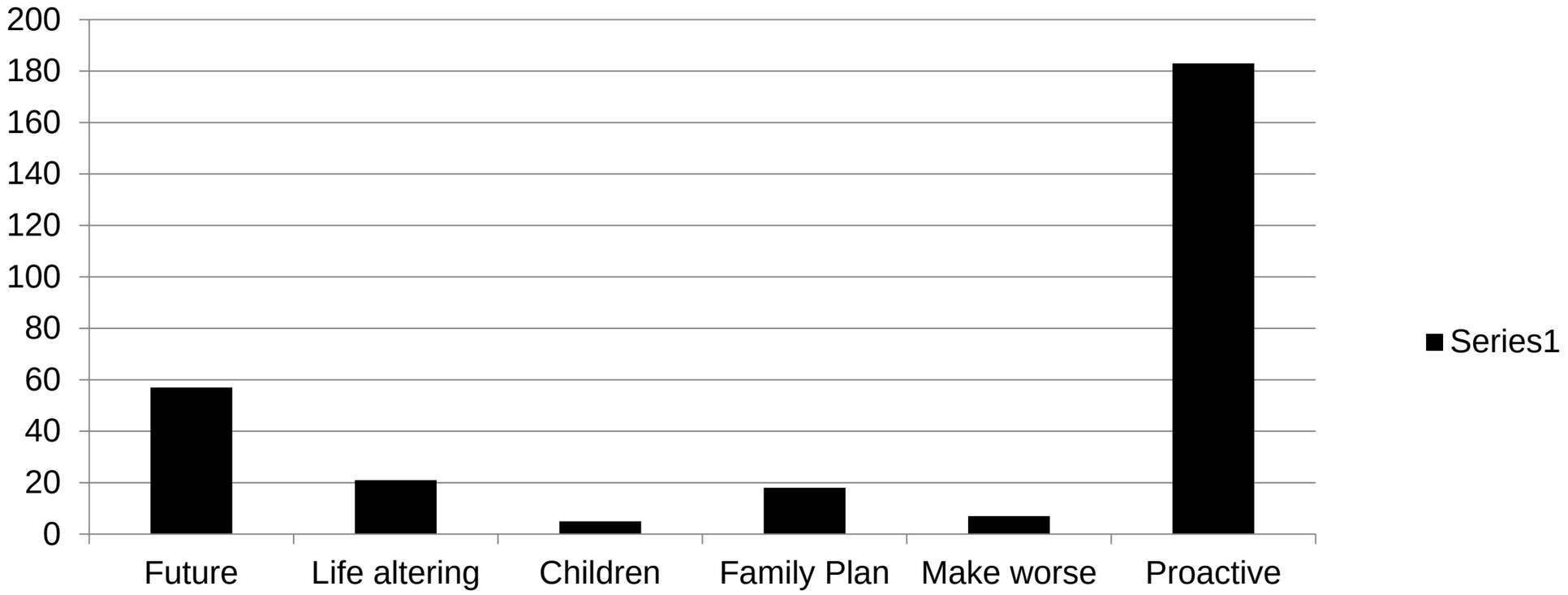
Declining to Participate

- 14.6% of families declined G4K enrollment
- 3.7% of families declined PG4KDS
- Compared patient variables among those declining genome sequencing to those declining PG4KDS
- Compared demographic of patient, mother, father and clinical factors
- Age, Sex, Race, Education, Income, Parental Martial Status, Spirituality, Number of Siblings, Interpreter Needed, Patient Diagnosis, Diagnosis Type
- Race/ethnicity differentiated study declination

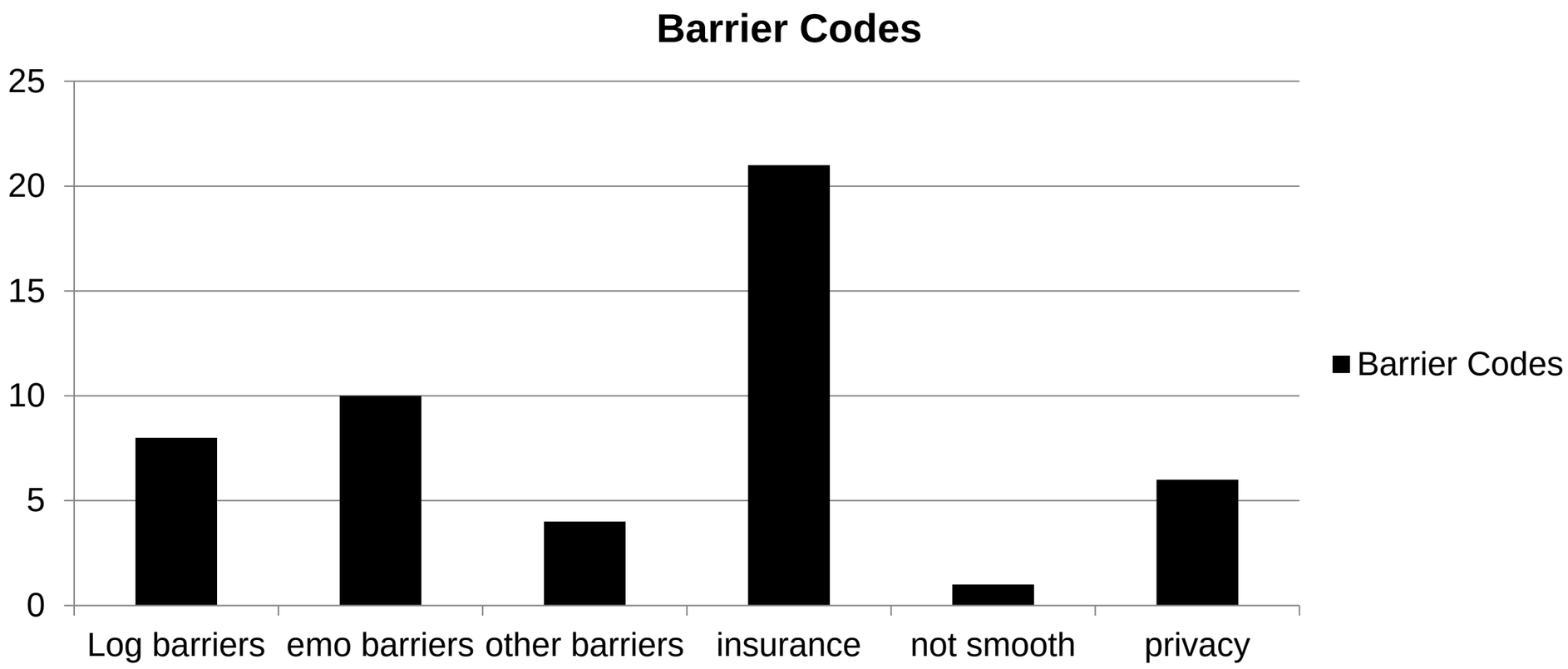
Cancer Families



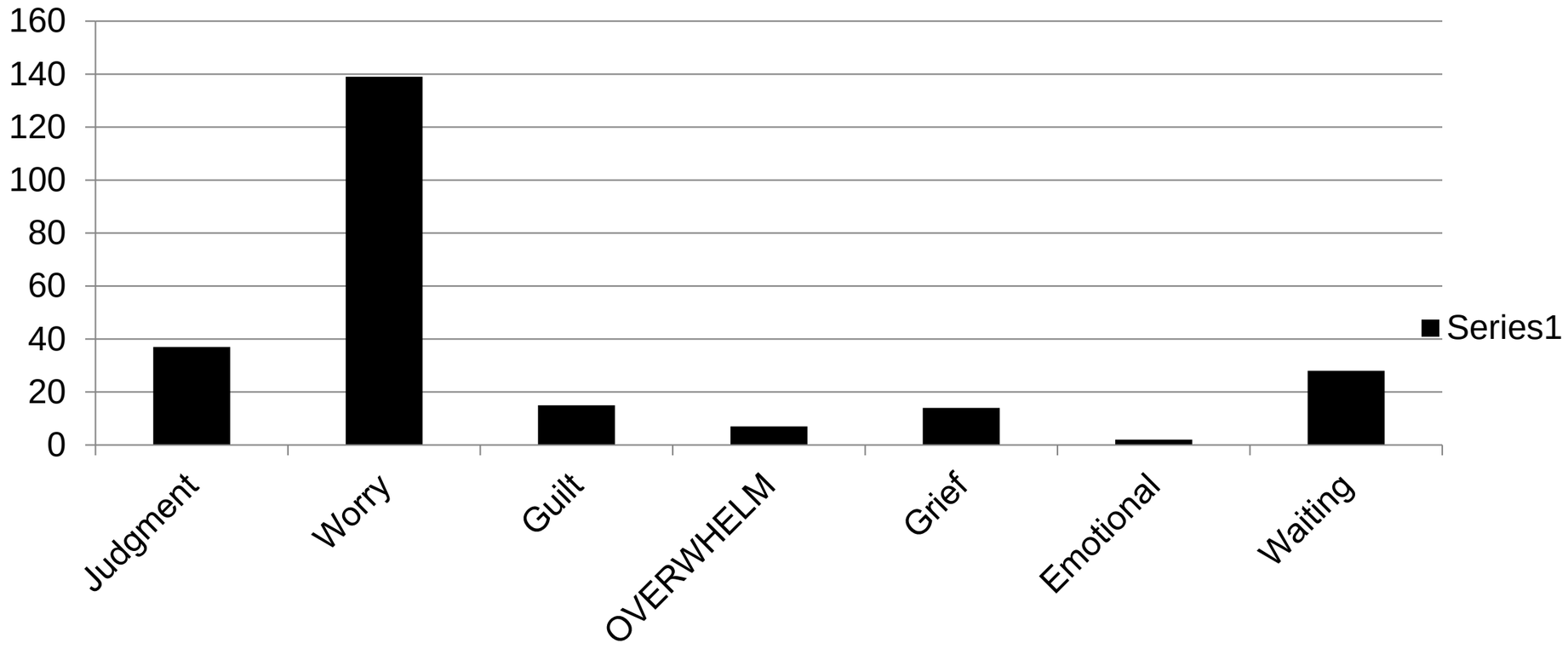
Parents Wanted Results and Forward Thinking



Reported Barriers



Testing Was Emotional



Study Conclusion

- Parents want the child involved as they felt was developmentally appropriate
- Parents express a connection between their family history of cancer, their child's diagnosis "Cancer Family"
- Parents want to have an answer so they can be Proactive
- While knowing is best they have worry

Parent-child communication surrounding genetic testing for Li-Fraumeni syndrome: Living under the cloud of cancer.
Valdez JM, Walker B, Ogg S, Gattuso J, Alderfer MA, Zelley K, Ford CA, Baker JN, Mandrell BN, Nichols KE.
Pediatr Blood Cancer. 2018 Nov;65(11):e27350. doi: 10.1002/pbc.27350. Epub 2018 Jul 15.

What We Have Learned

- Health-care providers lack confidence in discussing somatic and germline findings
- Physicians report the importance of trained health care providers including genetic APNs and genetic counselor in assisting with return of results
- Parents have expressed genomic sequencing as fulfilling their parental duty, wanting to be proactive

What We Have Learned

- Parents report barriers including insurance, privacy, logistics
- Want to be contacted with change in report
- Race/ethnicity are associated with decline in participation
- Patients and families are altruistic

Lessons Learned

-Collaboration
-Data Sharing
-Data Analysis
-Technology Development
-Societal Implications
-Flexible

The Role of Nursing in Genomic Precision Health

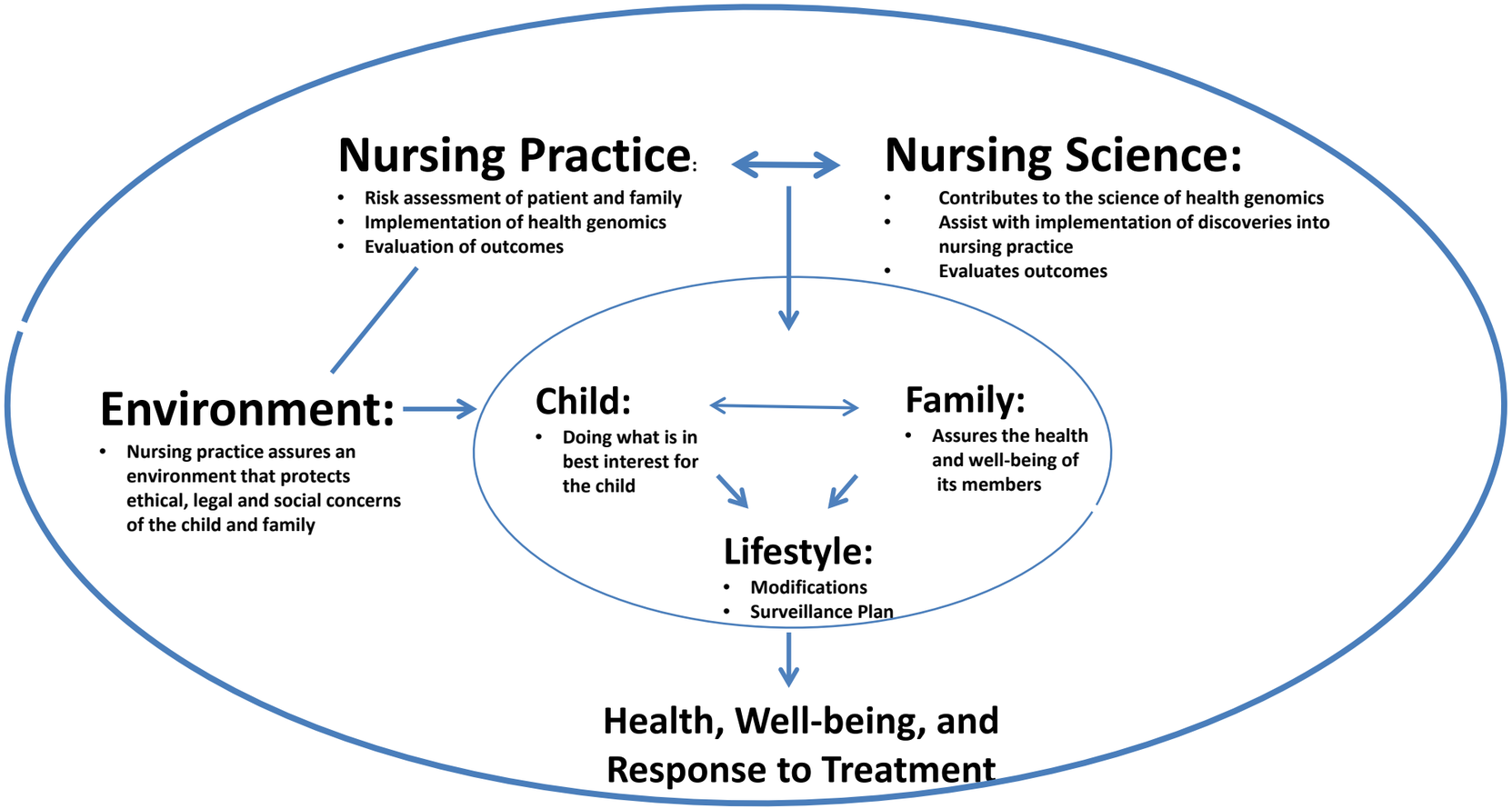


Figure 1: Influence of Nursing Science and Nursing Practice on the Health-care Environment, Improving Health, Well-Being and Response to Treatment for the Child and Family

Questions?

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