Pediatric Oncology Providers' Opinions on the Addition of Pediatric Cancer Syndromes to Wisconsin Newborn Screening

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BACKGROUND

The Wisconsin newborn screen (NBS) currently tests approximately 60,000 infants born in Wisconsin each year for 47 different congenital conditions using dried blood specimens, based on recent NBS data from 2020. The goal of NBS is to detect certain genetic disorders early in life to improve outcomes. Annually, the Wisconsin NBS detects approximately 125 affected infants.

Over 50 years ago, the World Health Organization (WHO) commissioned a report to assess the principles and practice of disease screening.[2] As technology continuously accelerates, the gap widens between what is technologically possible and what is practically and ethically feasible. This report proposed 10 criteria that stakeholders ought to consider for addition of a genetic disorder to the population (Table 1) and is referred to as the Wilson and Jungner classic screening criteria. These criteria help stakeholders weigh the benefits of early identification of disease with the potential costs, both monetary, physical, and psychosocial. In Wisconsin, the Secretary of the Wisconsin Department of Health Services has established a process by which individuals or groups can nominate a condition for NBS.

Each year, ~280 children will develop cancer in Wisconsin.[4] Survival rates have improved over time, however, cancer remains the leading cause of non-accidental death in children.[5] While most cancers are sporadic, germline pathogenic variants in pediatric genetic cancer predisposition syndrome (PGCPS) genes are thought to contribute to at least 8.5% of childhood cancers.[6,7] Based on disease incidence, approximately 66 infants could be identified annually with the addition of the ten most common childhood cancer syndromes to the Wisconsin NBS.

The goal of this study is to gather expert opinions of Wisconsin pediatric oncology providers to the proposed addition of these PGCPS to the NBS. Expert testimonies will provide important considerations for potential implementation.

METHODS

Sampling Frame

The sampling frame included pediatric oncology physicians located at five pediatric oncology centers in Wisconsin, including the University of Wisconsin-American HospFamily Children's Hospital (UW-AFCH), Children's Hospital of Wisconsin (CHW), Marshfield Children's ital (MCH), St. Vincent Pediatric Hematology and Oncology (St. Vincent), and Gunderson Health System Pediatric Cancer and Blood Disorders (GHS).

Survey Instrument Development

A survey was developed to ascertain pediatric cancer providers' experience, attitudes, and concerns regarding the addition of PGCPS to the Wisconsin Newborn Screen.

Survey Administration

Representatives from each of the five hospital systems were identified and contacted via email to participate in the study and to distribute the survey to members of their pediatric oncology teams. A reminder email was sent the following month. The survey was open from December 2020 to January 2021.

Data Analyses

General frequency responses for survey items were evaluated. The University of Wisconsin-Madison institutional review board deemed this project exempt (2020-1334).

Syndrome	Genes	Birth Incidence	Case/ Year	Cancer Spectrum	Other Phenotypes	% de novo
Neurofibromatosis Type 1	NF1	1/2700	25	• Neurofibromas • CNS tumors • Peripheral nerve sheath tumors • Breast cancer • Leukemia • Others	• Skin lesions • Learning disorders • Macrocephaly • Hypertension • Scoliosis • Others	50%
Tuberous Sclerosis	TSC1, TSC2	1/5800	12	• CNS tumors • Renal angiomyolipoma • Renal cell carcinoma • Cardiac rhabdomyoma • Others	• Seizures • Intellectual disability • Cortical dysplasia • Skin lesions • Retinal hamartoma • Lymphangio-leiomyomatosis • Others	66%
Autosomal Dominant Familial Adenomatous Polyposis	APC	1/8000	8	• Colorectal carcinoma • Other GI tumors • Hepatoblastoma • Thyroid cancer • Medulloblastoma • Desmoid tumors	• Colonic polyps • CHRPE • Osteomas • Dental abnormalities	20-25%
Li Fraumeni Syndrome	P53	1/10000	7	• Soft tissue sarcoma • Osteosarcoma • Breast cancer • Brain tumors • Adrenocortical tumors • Leukemia • Others		7-20%
Gorlin Syndrome	PTCH1, SUFU	1/19000	4	• Basal cell carcinoma • Medulloblastoma • Cardiac and ovarian fibroma	• Jaw keratocysts • Palmar/plantar pits • Ocular abnormalities • Dysmorphic features • Skeletal anomalies	30%
Multiple Endocrine Neoplasia I	MEN1	1/30000	2	• Endocrine tumors (parathyroid, gastro-entero-pancreatic tract, carcinoid, and adrenocortical) • Angiofibromas • Lipomas • Meningiomas • Leiomyomas		10%
Neurofibromatosis Type 2	NF2	1/33000	2	• Schwannomas (vestibular nerve and other cranial/peripheral nerves) • Meningioma • Ependymoma • Astrocytoma	• Skin lesions • Retinal hamartoma • Lens opacity • Peripheral neuropathy	50%
von Hippel Lindau Syndrome	VHL	1/33000	2	• Hemangioblastomas (brain, spinal cord, and retina) • Renal cell carcinoma • Pheochromocytoma • Paraganglioma • Neuroendocrine tumors • Endolymphatic sac tumors	• Renal cysts • Pancreatic cysts • Epididymal cysts • Broad ligament cysts	20%
Retinoblastoma	RB1	1/33000	2	• Retinoblastoma • Pinealoma • Osteosarcoma • Soft tissue sarcomas • Melanoma		75%
Multiple Endocrine Neoplasia II	RET	1/35000	2	• Medullary thyroid cancer • Pheochromocytoma (MEN2A/MEN2B) • Parathyroid adenoma (2B)	• Mucosal neuromas (2B) • Dysmorphic features (2B) • Ganglioneuromatosis of the gastrointestinal tract (2B)	5/50%

Successful development of a cancer **newborn screening** (NBS) program in Wisconsin could set a precedent for other states to develop similar NBS programs for **pediatric genetic cancer predisposition syndromes** (PGCPS). Widespread development of PGCPS screening programs could identify approximately **4,000 newborns** each year across the United States.

RESULTS

Respondent Characteristics

The survey had twelve total responses, and not every respondent answered every survey question. Of 11 respondents, 10 (90.9%) were MDs and 1 (9.1%) had an MS. Most of the respondents (81.8%) did not have specialized training in genetics, but all respondents had worked at least 2 years specifically in pediatric oncology

Positions on the Addition of Pediatric Cancer Syndromes

NF1 is the most prevalent pediatric cancer syndrome on the proposed list of conditions. 11 of 12 respondents (91.7%) "strongly agree" that NF1 should be added to the WI NBS. The most commonly chosen reasons for the addition were that early detection could lead to reduction in morbidity (90%), there are treatment or screening options available (90%), and screening for these conditions would be beneficial for the child (90%). Reasons cited for NF1 not to be added to the WI NBS included families' need for information and support could overwhelm an already limited capacity for genetic counseling and comprehensive care (n=1), identifying a condition in infancy that may not present until later in childhood leads to parents treating that child differently (n=1), and the anxiety/stress of reporting these conditions to families outweighs the potential benefits (n=1).

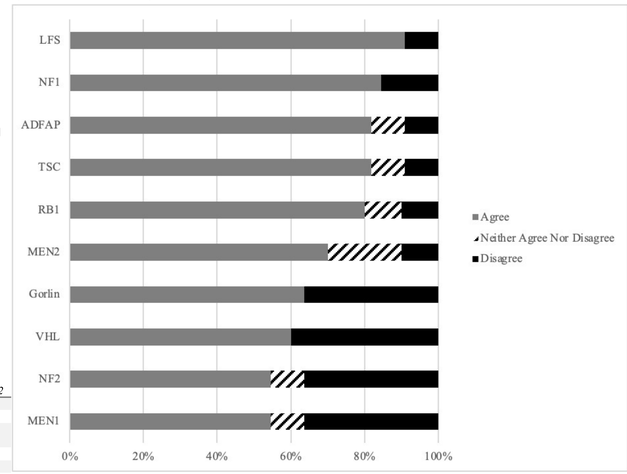
Of the remaining 9 conditions, 5 of the 11 respondents "strongly agree" with the addition of Autosomal Dominant Familial Adenomatous Polyposis Syndrome (ADFAP), Li Fraumeni Syndrome (LFS), and Retinoblastoma (RB1). 10 of 11 respondents agree to some extent that LFS should be added. 9 of 11 respondents agree to some extent that Tuberous Sclerosis (TSC), ADFAP, and RB1 should be included. Gorlin syndrome, Neurofibromatosis Type 2 (NF2), Multiple Endocrine Neoplasia Type 1 (MEN1) and von Hippel Lindau (VHL) had greater than 25% of respondents indicating that they disagree to some extent with their addition to the NBS.

Figure 2. Reasons cited for agreement with addition to the Wisconsin Newborn Screen.

	NF1	*TSC*	*FAP*	*LFS*	*Gorlin*	*MEN1*	*NF2*	*VHL*	*RB1*	*MEN2*
Birth Incidence	6	2	0	1	1	1	2	9	1	2
De novo rate	2	2	1	1	1	1	1	1	1	1
Early detection could lead to morbidity reduction	9	6	8	7	6	4	6	5	8	7
Reproductive decisions	3	4	3	5	2	3	2	2	4	2
Identify at-risk family members	8	5	5	6	4	4	4	5	5	4
Patients' families would want to know if their child was at risk	4	4	5	5	4	4	4	4	5	4
Beneficial for the child	9	8	7	7	6	5	4	4	6	5
Beneficial for the parents	4	4	4	4	4	4	3	3	2	3
Treatment/screening options available	9	6	8	6	5	4	3	4	6	5
Other	1	0	0	0	0	0	0	0	0	0

Note: Numbers in table columns correspond to the number of respondents.

Figure 1. Extent to which respondents agree or disagree with the addition of ten pediatric cancer syndromes.



CONCLUSIONS

Next Steps

A cost-benefit analysis will need to be completed in addition to assay development for the proposed 12 gene panel in order to determine the economic and technical feasibility of screening approximately 60,000 infants born annually in Wisconsin.

Furthermore, establishing comprehensive multidisciplinary clinics could aid in diagnosis and treatment of children and families identified through the WI NBS for PGCPS. In addition to the established cancer risks for these PGCPS, the natural history for the two most common syndromes proposed include other health problems which could be mitigated with early identification through NBS.

Finally, research to gather more opinions of stakeholders within the state of Wisconsin and other geographic regions is currently underway.

Conclusion

Successful development of a cancer NBS program in Wisconsin could set a precedent for other states to develop similar NBS programs for PGCPS. Widespread development of PGCPS screening programs could identify approximately 4,000 newborns each year across the United States. Furthermore, the development of a multi-gene panel and RNA sequencing for NBS would open the possibility of screening for non-cancer genetic disorders that affect newborns and children. As genetic testing through gene and RNA-based sequencing becomes economically feasible, these conditions could be tested concomitantly with the current NBS protocol via postnatal blood spot.

ADDITIONAL KEY INFORMATION

Considerations for Pediatric Cancer Syndromes

Respondents also shared to what extent they agree or disagree with statements that pertain to the differences between the genetic disorders which are currently on the Wisconsin newborn screen and the proposed pediatric cancer syndromes. 11 out of 12 respondents felt that given that this set of disorders are inherited in an autosomal dominant pattern, screening for these conditions would be beneficial for identifying the genetic conditions, as well as beneficial for identifying parents with genetic cancer syndromes. However, only 8 of 12 respondents believe that screening for these conditions would be beneficial for the child when considering that these autosomal dominant conditions often demonstrate incomplete penetrance, and 11 of 12 felt that identifying a condition in infancy that may not present until later in childhood leads to parents treating that child differently. In considering the age of onset and availability of treatment and screening recommendations, none of the respondents disagreed with the statement that early detection of these cancers is effective in reducing the morbidity of these conditions.

Familial Implications

10 of 12 respondents felt that knowing a diagnosis as early as possible is important for the family to make reproductive decisions and that most of their patients' families would want to know if their child was at risk for a childhood cancer. Still, 4 out of 12 respondents "somewhat agree" that the anxiety/stress of reporting these conditions to families outweighs the potential benefits.

Additional Considerations

- Approximately half of children identified through the NBS for PGCPS may have additional undiagnosed family members who would benefit from genetic testing.
- Newborn screening through targeted next generation screening can also result in ambiguous test results or variants of uncertain significance (VUSes). Some VUSes may eventually be reclassified, but a protocol for reporting out VUSes and/or reclassified variants would need to be developed.
- Implementation may also create geographic inequity, as residents in surrounding states may not have equal access to their newborns' pediatric genetic cancer risks. While the conditions screened by state NBS are ultimately decided by the individual states themselves, consideration should be given to the possible inequities these differences may construct.

Limitations

One limitation of this study was the small sample size of respondents. This response rate may be due to the timing of survey administration during the height of the COVID-19 pandemic in Wisconsin and in the United States. Future studies could include expanding survey distribution to all pediatric providers in Wisconsin, genetic counselors in Wisconsin, and/or related providers nationwide. Additionally, opinions and attitudes of Wisconsin families who would potentially participate in the broadened NBS program should be evaluated in order to ensure that the screen is acceptable to the population.

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