Genetics in Medicine

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BRIEF COMMUNICATION

Universal newborn genetic screening for pediatric cancer predisposition syndromes: model-based insights

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PURPOSE: Genetic testing for pediatric cancer predisposition syndromes (CPS) could augment newborn screening programs, but with uncertain benefits and costs.

METHODS: We developed a simulation model to evaluate universal screening for a CPS panel. Cohorts of US newborns were simulated under universal screening versus usual care. Using data from clinical studies, ClinVar, and gnomAD, the presence of pathogenic/likely pathogenic (P/LP) variants in *RET*, *RB1*, *TP53*, *DICER1*, *SUFU*, *PTCH1*, *SMARCB1*, *WT1*, *APC*, *ALK*, and *PHOX2B* were assigned at birth. Newborns with identified variants underwent guideline surveillance. Survival benefit was modeled via reductions in advanced disease, cancer deaths, and treatment-related late mortality, assuming 100% adherence.

RESULTS: Among 3.7 million newborns, under usual care, 1,803 developed a CPS malignancy before age 20. With universal screening, 13.3% were identified at birth as at-risk due to P/LP variant detection and underwent surveillance, resulting in a 53.5% decrease in cancer deaths in P/LP heterozygotes and a 7.8% decrease among the entire cohort before age 20. Given a test cost of $55, universal screening cost $244,860 per life-year gained; with a $20 test, the cost fell to $99,430 per life-year gained.

CONCLUSION: Population-based genetic testing of newborns may reduce mortality associated with pediatric cancers and could be cost-effective as sequencing costs decline.

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INTRODUCTION

Universal newborn screening (NBS) has successfully decreased the morbidity and mortality of a wide range of severe pediatric-onset diseases including phenylketonuria, cystic fibrosis, and sickle cell disease.[1] Genetic testing has the potential to augment universal NBS programs, and research exploring the medical, technological, public health, and ethical implications of universal newborn genetic screening is ongoing.[2,3] Detection of germline pathogenic variants in genes associated with a high risk of early childhood tumors could be incorporated into expanded NBS programs; variant detection would prompt application of accepted clinical care recommendations currently utilized by pediatric oncologists for infants and children with known cancer predisposition syndromes (CPS).[4]

Decision modeling can evaluate the potential of genetic testing in NBS, as it can facilitate evidence synthesis, provide data to inform clinical guidelines,[5,6] and evaluate new diseases for inclusion in NBS.[7] This is especially useful in settings of rare diseases, like pediatric cancer, where sufficiently powered randomized clinical trials that test the clinical utility of NBS for early onset disease would be difficult. Using a decision-analytic framework, we asked: *what are the potential clinical benefits, harms, and cost-effectiveness of newborn genetic screening, using a targeted next-generation sequencing (t-NGS) approach for a select panel of genes associated with early onset childhood cancer?*

MATERIALS AND METHODS

We developed the Precision Medicine Policy and Treatment (PreEMPT) model to estimate the potential risks and benefits of population-based genetic screening for pathogenic germline variants in *RET*, *RB1*, *TP53*, *DICER1*, *SUFU*, *PTCH1*, *SMARCB1*, *PHOX2B*, *ALK*, *WT1*, or *APC*. These autosomal dominant cancer predisposition genes were selected because of their association with very early onset malignancy and the availability of surveillance guidelines for early detection starting in infancy[8–14] (Table 1). Using data from clinical studies, ClinVar,[15] the Genome Aggregation Database (gnomAD),[16] and the US Surveillance, Epidemiology and End Results (SEER) Program,[17] we assigned each newborn a probability of carrying a pathogenic or likely pathogenic (P/LP) variant in each of the 11 genes (*RET* variants were restricted to those for multiple endocrine neoplasia type 2B [MEN2B][18]). We limited variants to high-quality P/LP variants identified in ClinVar (i.e., 2-star) and confirmed the list via curation by the Mass General Brigham Laboratory for Molecular Medicine (Supplemental Tables 1, 2). The prevalence of P/LP variants was based on best available data from clinical studies for cancer cases and gnomAD data for noncancer cases (Supplemental Table 3). For genes without any P/LP variants in gnomAD, we assumed an allele frequency of 0.5 among the 282,912 alleles in gnomAD. We assumed that the occurrence of P/LP variants were independent and summed allele frequencies across all variants for each gene. Using Bayes' theorem to synthesize data on the proportions of individuals with and without P/LP variants and who develop each cancer before age 20, we estimated the penetrance for each gene, defined as the probability an individual carrying a P/LP variant will develop a condition before age 20. See Supplemental Materials for additional details.

Cohorts of newborns representative of a modern US birth cohort were simulated under the scenarios of usual care and t-NGS at birth and followed throughout their lifetimes (Supplemental Fig. 1). Under t-NGS, we assumed newborns with identified P/LP variants would undergo cancer surveillance based on established guidelines (Table 1). As a best-case estimate of program efficacy, we assumed 100% adherence with t-NGS screening and surveillance recommendations.

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Table 1. Pediatric cancer predisposition syndrome (CPS) genes and surveillance recommendations.

Gene	Cancer	Surveillance benefit	Surveillance recommendation (for primary tumor)	Reference
RET	Medullary thyroid carcinoma	Primary prevention (thyroidectomy in first years of life)	Prophylactic thyroidectomy[a]	8
RB1	Retinoblastoma (hereditary)	Stage shift, avoid blindness through avoidance of enucleation, reduce chemo/radiotherapy exposure	Eye exam: frequency varies by age, ranging from every 2 to 4 weeks from birth to 8 weeks to every 6 months starting at 48 months; sedation between 8 weeks to 60 months.	9
TP53	Adrenocortical carcinoma Choroid plexus Rhabdomyosarcoma Osteosarcoma	Stage shift, increased survival, avoidance of radiotherapy	US of abdomen and pelvis: from birth to age 18, every 3 to 4 months. Brain MRI: from birth to age 18, every 1 year.	10
SMARCB1	Rhabdoid tumors	Stage shift, increased survival (these are only curable if fully resected)	US of abdomen/kidneys: birth to age 5, every 3 months. Brain MRI: birth to age 5, every 3 months.	11
DICER1	Pleuropulmonary blastoma	Stage shift, increased survival, avoidance of radiotherapy	Chest X-ray: from 3 months to 8 years, every 6 months; from 8 to 12 years, every 1 year. Chest CT: once at 3–6 months old; repeat at 2.5–3 years old.	12
SUFU, PTCH1	Medulloblastoma	Stage shift, reduction of therapeutic intensity, increased survival,	Brain MRI: from birth to 3 years, every 4 months; from 3 to 5 years, every 6 months.	11
PHOX2B, ALK	Neuroblastoma	Stage shift, increased survival, avoidance of radiotherapy	US of abdomen: from birth to 6 years, every 3 months; from 6 to 10 years of age: every 6 months. Chest X-ray: from birth to 6 years, every 3 months; from 6 to 10 years of age: every 6 months.	9
WT1	Wilms tumor	Stage shift, nephron sparing surgeries, avoidance of radiotherapy	US of abdomen: from birth to 5 years of age, every 4 months.	13
APC	Hepatoblastoma	Stage shift, avoidance of radiotherapy, reduced need for liver transplant, increased survival	US of abdomen: from birth to 7 years of age, every 6 months.	14

CT computed tomography, *MRI* magnetic resonance imaging, *US* ultrasound.
[a]Recommended routine surveillance also serial ultrasounds and biochemical monitoring of serum calcitonin levels for early detection of later-onset tumors (not modeled).

Utilizing SEER data and published literature to estimate incidence, stage distribution, and outcomes, newborns were at risk for each cancer of interest (those associated with the 11 CPS). Treatment by stage for each diagnosis was based on standard care and included radiation and chemotherapy when indicated (Supplemental Table 4). Individuals who received chemotherapy and/or radiation as part of cancer treatment faced excess late mortality risks as adults starting at age 20 based on the Childhood Cancer Survivor Study.[19,20] Newborns found to be heterozygotes of P/LP variants underwent surveillance, which resulted in early detection of malignancy, which, for specific cancers, resulted in reduced use of radiation and/or chemotherapy and improved outcomes (Table 1). Clinical benefit for t-NGS and associated surveillance was modeled as reductions in advanced disease, cancer deaths, and treatment-related late mortality.

Costs were estimated for direct medical costs, patient time costs, and genetic testing (for the t-NGS strategy) (Supplemental Table 5). For t-NGS, we assumed a cost of $55 for the 11-gene panel test (i.e., $5 per gene) based upon expert input, current cost of NBS, and commercial cost for a panel test.[21] We assumed that this cost reflected the incremental cost of adding the panel to a NBS program with existing infrastructure for genetic testing. Costs for surveillance and cancer treatment were based on published estimates and national databases. To account for patient time costs, we included parental time lost from work (see Supplemental Materials). All costs were expressed in 2018 dollars.

To capture uncertainty, we conducted 1,000 simulations in which each parameter was sampled from its underlying distribution and report the mean and 95% uncertainty interval (UI) for all outcomes. Given the goals of improving child health, the model did not include impact of early detection of adult-onset malignancy, which is increased in some CPS (for example, *TP53*), or impact on family member health/reflex genetic testing.

To assess the potential harms associated with t-NGS, most prominently the burden of a genetic diagnosis in the absence of a pediatric cancer occurrence, we defined individuals with P/LP variants who developed cancer before age 20 (true positives) as having "penetrant variant status" (PVS) and individuals with P/LP variants who did *not* develop cancer by age 20 as having "nonpenetrant variant status" (NPVS). This allowed us to illustrate the harm–benefit tradeoffs associated with t-NGS by estimating the number of NPVSs per PVS, cancer death averted, and life-year (LY) gained in the cohort.

To assess the cost-effectiveness of genetic CPS screening, we calculated an incremental cost-effectiveness ratio (ICER), defined as the additional cost of t-NGS divided by its additional clinical benefit compared with usual care, expressed as cost per LY gained. Although higher cost-effectiveness thresholds have been suggested for rare diseases,[22] we estimated the threshold cost for the 11-gene panel test at which t-NGS would achieve an ICER of <$100,000 per LY gained as changes in technology will likely impact costs.

Sensitivity analyses examined the influence of assumptions on P/LP variant prevalence among cancer and noncancer cases, adherence to guideline surveillance, and surveillance and cancer treatment costs, as well as stage-specific estimates of 5-year survival, the proportion of cancers diagnosed as advanced disease, and excess mortality risks associated with cancer treatment.

RESULTS

In a typical US birth cohort of 3.7 million newborns, the model estimated 1,803 individuals would develop a CPS-associated cancer before age 20 (95% UI, 1,756 to 1,850), 13.3% of whom would have P/LP CPS variants (95% UI, 11.3% to 15.7%). Under t-NGS, 1,584 individuals with P/LP CPS variants (95% UI, 1,230 to 2,026) would be identified, 232 (95% UI, 196 to 278) of whom would develop cancer before age 20 (i.e., PVS) and 1,353 (95% UI, 991 to 1,788) would not (i.e., NPVS). This resulted in an estimated positive predictive probability, or penetrance, of 14.8% (95% UI, 11.2% to 19.6%) for the 11-gene panel and a relative risk of developing a cancer before the age of 20 of 351 (95% UI, 260 to 468) among individuals with P/LP variants. Penetrance and relative risk estimates varied for individual genes (Table 2). In terms of clinical benefit, the model estimated that compared with usual care, t-NGS would reduce cancer deaths before age 20 overall by 7.8% (95% UI, 5.8% to 10.1%) and decrease the proportion of 5-year survivors at risk for radiation-related excess mortality by 5.8% (95% UI, 3.6% to 8.6%) (Table 2). Additionally, t-NGS would increase the number of adult cancer survivors alive at age 45 by 2.1% (95% UI, 1.4 to 2.9%), and result in a gain of 2,937 (95% UI, 2,244 to 3,879) LY. The estimated benefit for all outcomes was considerably higher among individuals with P/LP variants (Fig. 1). For example, among P/LP heterozygotes, t-NGS would reduce cancer deaths before age 20 by 53.5% (95% UI, 47.1% to 60.5%). In terms of harm–benefit tradeoffs, for t-NGS, the number with NPVS identified per PVS was 5.9 (95% UI, 4.1 to 7.9), the number of NPVS per cancer death averted was 43.5 (95% UI, 29.1 to 61.5), and the number of NPVS per LY gained was 0.5 (95% UI, 0.3 to 0.7). Compared with usual care, t-NGS had an ICER of $244,860 per LY gained (95% UI, $181,500/LY to $327,520/LY) assuming a 11-gene panel cost of $55 per newborn. At a panel cost of $20, the ICER fell to $99,430 per LY (95% UI, $72,510/LY to $137,330/LY).

Cost-effectiveness of t-NGS was most sensitive to P/LP variant prevalence among cancer cases and differences in 5-year survival rates for localized versus advanced disease, moderately sensitive to the proportion of cancers diagnosed with advanced disease and the P/LP variant prevalence among controls, and robust to assumptions on surveillance and cancer treatment costs (Supplemental Fig. 2). With less than full adherence to surveillance guidelines, the ICER for t-NGS increased to $270,260/LY with 90% compliance (95% UI, $201,160/LY to $361,210/LY) and $321,000/LY with 70% compliance (95% UI, $240,480/LY to $428,720/LY).

DISCUSSION

Leveraging data from ClinVar, gnomAD, SEER, and published literature, we used a model-based approach to estimate the potential clinical impact of universal genetic screening in newborns for pediatric CPS. Our findings suggest that under the best-case assumption of full adherence to screening and surveillance guidelines, t-NGS would identify approximately 1,580 individuals with P/LP CPS variants among 3.7 million newborns each year in the United States. If these newborns were evaluated, underwent genetic counseling, and offered cancer surveillance, more than half of cancer deaths among individuals with CPS variants would be averted. Further, as the costs of genetic screening decline, targeted newborn screening for pediatric cancer genes could be cost-effective given benchmarks for "good value."[23]

Newborn screening for any disorder requires balancing the potential benefits (prevention or early detection of disease) and harms (unnecessary surveillance costs and parental anxiety). Inclusion of genetic testing for CPS risk as part of NBS programs will present new uncertainties, most importantly with respect to the "allowable" burden of tests detecting P/LP variants of unknown or low penetrance (e.g., parents who are told that the infant is at increased risk of cancer, but cancer may not manifest in childhood or at all). While we modeled 11 CPS genes as a panel, analyses on individual or subsets of genes can guide efforts to reduce potential harm by identifying genes with higher penetrance (e.g., *RB1*) or where the benefit is well understood (*RET*). Of importance, in our study, we assumed that the CPS test would be included as part of state-wide NBS programs, after completion of successful pilot testing. We recognize, however, that the process of adding new tests is complex and varies by state. In an alternative model, separate consent for this test (outside of usual NBS) would create added burden and require additional resources for implementation not reflected in our study.

While we provided estimates of the potential harm–benefit tradeoffs, we did not account for the impact of this knowledge on families, as well as other potential impacts of testing, such as risk of adult-onset cancer, family reproductive planning, and detection of cancer risk in family members; future studies should consider these important factors. Available data from families with CPS suggest that entering a child into a surveillance protocol based

Table 2. Estimated clinical validity of t-NGS for genes associated with pediatric CPS[a] in a 3.7 million newborn cohort (US birth rate annual).

Gene(s)[b]	Clinical validity, mean (95% UI)					Clinical utility, mean (95% UI)					
	t-NGS results			Penetrance by age 20, %	Relative risk (RR) of cancer before age 20 among individuals with P/LP variants[c]	Cancer deaths		5-year survivors at risk for radiation-related late mortality		5-year survivors alive at age 45	
	Penetrant variant status, *n*	Nonpenetrant variant status, *n*	Individuals without P/LP variants who develop cancer before age 20, *n*			Usual care	% reduction with t-NGS	Usual care	% reduction with t-NGS	Usual care	% increase with t-NGS
11-gene panel	232 (196–278)	1,353 (991–1,788)	1,563 (1,501–1,625)	14.8 (11.2–19.6)	351 (260–468)	406 (383–428)	7.8 (5.8–10.1)	701 (673–729)	5.8 (8.6– 3.6)	1,254 (1,215–1,292)	2.1 (1.4–2.9)
Single genes											
ALK	12 (1–33)	16 (1–66)	467 (439–496)	48.2 (7.9–96.0)	3,844 (597–7,699)	93 (81–104)	2.8 (0.5–6.7)	288 (269–308)	3.2 (7.6–0.7)	343 (322–365)	1.0 (0.2–2.4)
PHOX2B	4 (0–14)	10 (0–62)	475 (449–502)	47.9 (5.6–100.0)	3,731 (444–7,785)						
APC	11 (3–21)	350 (187–565)	97 (84–110)	3.2 (0.9–6.8)	1,247 (330–2,817)	21 (16–26)	4.9 (1.2–10.6)	44 (38–51)	9.5 (18.5–2.8)	78 (69–87)	1.5 (0.4–3.2)
DICER1	6 (4–10)	87 (17–202)	2 (0–4)	9.3 (2.4–27.9)	336,411 (34,992–1,705,669)	2 (1–4)	69.9 (38.5–94.4)	3 (1–5)	70.2 (92.0–41.4)	6 (3–9)	29.5 (10.3–58.0)
RB1	68 (59–78)	29 (1–113)	6 (3–10)	75.3 (37.3–98.6)	542,024 (204,729–1,201,835)	2 (1–3)	62.2 (37.5–92.9)	20 (16–24)	90.6 (96.2–83.6)	68 (60–77)	4.1 (2.5–5.9)
SMARCB1	25 (17–34)	13 (0–67)	47 (37–57)	74.6 (27.3–99.6)	60,081 (21,644–90,587)	45 (39–51)	13.9 (7.9–21.7)	27 (22–32)	23.1 (13.8–34.7)	23 (19–28)	23.1 (13.5–35.6)
SUFU	17 (7–29)	15 (2–56)	79 (66–93)	60.2 (24.2–89.3)	28,223 (10,812–43,135)	34 (29–40)	15.9 (10.4–22.1)	62 (53–71)	8.8 (5.7–12.4)	54 (47–61)	8.8 (5.6–12.7)
PTCH1	17 (7–28)	15 (2–59)	79 (66–94)	60.0 (24.4–88.6)	28,168 (11,545–42,971)						
TP53	62 (36–100)	765 (496–1,074)	501 (458–536)	7.7 (4.2–13.0)	572 (297–1,013)	26 (16–39)	50.5 (40.9–59.9)	16 (6–29)	87.3 (96.0–71.8)	377 (357–397)	3.4 (1.9–5.7)
WT1	9 (3–18)	13 (0–65)	386 (361–409)	56.8 (8.8–100.0)	5,452 (835–9,771)	29 (22–36)	1.1 (0.0–2.9)	200 (184–216)	1.6 (3.2–0.5)	325 (304–344)	0.1 (0.0–0.3)

CPS cancer predisposition syndromes, *P/LP* pathogenic/likely pathogenic, *t-NGS* targeted next-generation sequencing, *UI* uncertainty interval.

[a]CPS-associated cancers include medullary thyroid carcinoma (*RET*), bilateral retinoblastoma (*RB1*), adrenocortical carcinoma (*TP53*), choroid plexus (*TP53*), rhabdomyosarcoma (*TP53*), osteosarcoma (*TP53*), rhabdoid tumors (*SMARCB1*), pleuropulmonary blastoma (*DICER1*), medulloblastoma (*SUFU, PTCH1*), neuroblastoma (*ALK, PHOX2B*), Wilms tumor (*WT1*), and hepatoblastoma (*APC*).

[b]*RET* results are not shown as P/LP variants were associated with prevention of cancer cases versus averted cancer deaths.

[c]Compared with individuals without P/LP variants.

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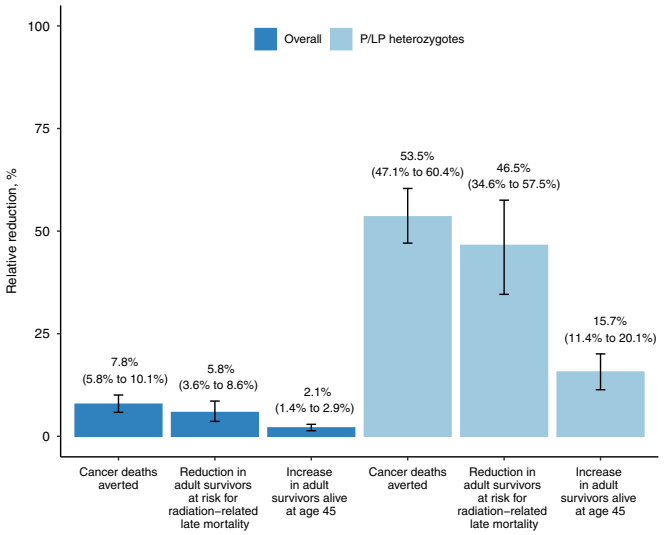

Fig. 1 Modeled clinical outcomes for targeted next-generation sequencing (t-NGS) vs. usual care. Shown are estimates for the overall cohort of 3.7 million screened newborns and among the subset of newborns with identified pathogenic/likely pathogenic (P/LP variants). The 95% uncertainty intervals among the 1,000 simulations are listed in the parantheses and shown by the bars.

upon genetic testing decreased anxiety and did not create an excessive burden.[24]

We assumed full adherence to surveillance recommendations to estimate the potential survival benefit of surveillance for CPS-associated pediatric cancers. As the cost-effectiveness of screening was less favorable with lower adherence, ensuring adherence will be crucial to realize the projected benefits. Of note, other benefits of early detection to avert toxicity (such as avoidance of blindness after early detection of retinoblastoma) were not captured in our model.

We assumed, in our cost estimates, that NBS will move forward nationally to establish infrastructure that supports genetic screening in general. Additional resources will be needed to build this capacity, as well as support for families after genetic information disclosure. The benefits of surveillance, as modeled in our study, are based upon scant data, but represent current recommendations for clinically detected children with CPS. The National Cancer Institute (NCI) Childhood Cancer Data Initiative aims to collect data on every child diagnosed with cancer in the United States and may provide more precise data in the coming years. Our model can readily incorporate these and other new data as they become available to generate updated estimates.

While our findings are suggestive, using newborn genetic screening for pediatric CPS as an example, our study demonstrates how advances in genetics can be applied to populations, and what the implications might be for public health. Prospective clinical studies that investigate crucial factors—such as parental uptake of testing, impact of a genetic CPS diagnosis on families, adherence to surveillance, and effectiveness of surveillance in preventing advanced disease—are necessary before this testing can be proposed as a component of population-based newborn screening.

DATA AVAILABILITY

Additional details about the Precision Medicine Policy and Treatment (PreEMPT) model, data used as model input parameters, and output data from the model are available by request from the corresponding author. A list of variants included in the modeling study is also provided in Supplemental Table 2.

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COMPETING INTERESTS

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ADDITIONAL INFORMATION

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SUPPLEMENTAL MATERIALS for:

Universal newborn genetic screening for pediatric cancer predisposition syndromes: model-based insights

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Supplemental Methods

Overview

We developed the Precision Medicine Prevention and Treatment (PreEMPT) Model to simulate the risk of 12 pediatric cancers associated with early onset pediatric malignancy in the setting of known autosomal dominant cancer predisposition syndromes (CPS). These CPS are associated with increased early onset cancer in the setting of germline pathogenic or likely pathogenic (P/LP) variants in *RET*, *RB1*, *TP53*, *DICER1*, *SUFU*, *PTCH1*, *SMARCB1*, *PHOX2B*, *ALK*, *WT1*, or *APC*. These CPS and genes were selected because they are associated with very high relative risks for the development of early childhood cancers for which cancer surveillance recommendations exist and are directed at early detection.

Using Bayes' theorem, in which a prior probability for developing a condition (pediatric malignancy in this case) is updated to a revised (posterior) probability that incorporates new genetic information,[1] we simulated the risk of developing each cancer based on the following data: i) prevalence of reported P/LP variants identified from studies of germline variants among specific childhood cancer cases, ii) prevalence of variants among controls (i.e. individuals without a cancer history) using population allele frequency data reported in Genome Aggregation Database (gnomAD; v2.1.1),[2] and iii) the risk of developing each CPS-associated cancer, based on data from the Surveillance, Epidemiology and End Results (SEER) Program[3]. This allowed us to estimate positive predictive probability (i.e., penetrance), negative predictive probability, and relative risk of disease given the presence of a variant. Pathogenic variants were determined using data from ClinVar,[4] including only 2-star variants which were classified as pathogenic (P) or likely pathogenic (LP) (i.e. high-quality) and subsequently re-evaluated for pathogenicity by experts at a clinical genetics testing laboratory using American College of Medical Genetics and Genomics (ACMG) criteria[5,6] modified for pediatric cancer genes (see additional details below).

Strategies and Analysis

Cohorts of newborns representative of a modern US birth cohort were simulated under Usual Care and t-NGS (**Supplemental Figure 1**). In the model, newborns are at risk for developing cancer before the age of 20 based on the presence (or absence) of P/LP variants. Once diagnosed, these individuals face stage-specific mortality risks with stage distribution based on SEER data. Under Usual Care, we assumed that a proportion of newborns would undergo genetic screening and surveillance due to family history and/or a known cancer predisposition syndrome, as reflected in SEER data. Under t-NGS, all newborns undergo sequencing and those with P/LP variants identified undergo cancer surveillance based on established guidelines for each gene-related pediatric malignancy[7-14] (**Table 1**). We assumed that under surveillance, all cancer cases would be diagnosed as localized (vs. advanced disease) with more favorable survival rates drawn from SEER outcomes for localized disease. Among P/LP heterozygotes for *RET*, cancer was preventable via prophylactic thyroidectomy. We assumed that diagnosis of localized disease would preclude the need for radiotherapy for all cancers except medulloblastoma and rhabdoid tumors (for which radiotherapy is standard therapy even at early stage). Clinical benefit for t-NGS was therefore modeled as a reduction in proportion of advanced disease, cancer deaths, and treatment-related late mortality risks. **Supplemental Table 2** summarizes the cancer data used to inform the simulation model.

Simulation model

At the start of the simulation, newborns enter the model and, based on the presence (or absence) of specific genetic variants identified via t-NGS, face age-specific risks of developing pediatric cancer. Individuals face stage-specific mortality risks once diagnosed. All individuals are at risk of dying from other causes of death, and individuals who received chemotherapy and/or radiation as part of

cancer treatment face excess late mortality risks as adult cancer survivors. Individuals are followed throughout the course of their lifetimes.

Estimating penetrance using Bayes' Theorem

The penetrance, defined as the probability an individual carrying a pathogenic (P)/likely pathogenic (LP) variant will develop a condition before age 20, was based on the following equation:

$$p(D+|M+) = \frac{[p(M+|D+) * p(D+)]}{p(M+)}$$

where $p(M+|D+)$ = proportion of individuals with the condition with a P/LP variant,
$p(D+)$ = proportion of newborns who will develop the condition before age 20, and
$p(M+)$ = prevalence of the P/LP variants in newborns (defined as the weighted average of $p(M+|D+)$ and $p(M+|D-)$, the proportion of individuals *without* the condition with a P/LP variant)

Prevalence of P/LP variants

Supplemental Table 1 summarizes the number of 2-star P/LP variants identified in ClinVar for each gene. The pathogenicity of the variants was confirmed by the Laboratory of Molecular Medicine at Partners HealthCare using criteria established by the ACMG[5,6] modified for pediatric cancer genes. Additional details on these variants are described in **Supplemental Table 2**. Among 477 P/LP variants identified in ClinVar, only 14 variants were reclassified as variants of uncertain significance.

The gnomAD database were queried for all 463 P/LP variants, with entries identified for 30 variants. For these variants, the reported allele frequencies were used to inform variant prevalence among non-cancer cases (i.e. controls) in the simulation model. *RET* variants were limited to those in exon 17 (M918T) and exon 15 (A883F) identified specifically for multiple endocrine neoplasia type 2B (MEN2B).[15] For genes without any P/LP variants identified in gnomAD, we assumed an allele frequency of 0.5 among the 282,912 alleles in gnomAD. We assumed that the occurrence of P/LP variants were independent and summed allele frequencies across all variants for each gene.

Supplemental Table 3 summarizes model inputs on the prevalence of pathogenic variants. For pediatric cancer cases, prevalence estimates were based on clinical studies.[16-28] For controls, defined as individuals who do not develop cancer before age 20, prevalence estimates were based on allele frequencies from gnomAD as described above.[2]

Cancer data

Supplemental Table 4 provides a summary of the cancer data used in the simulation model. For each cancer, age-specific incidence was based on the U.S. Surveillance, Epidemiology, and End Results (SEER) Program.[3] Stage distribution at diagnosis was categorized as localized or advanced disease (defined as regional, distant and unstaged tumors). Due to limited data among variant heterozygotes, we assumed that stage distribution was similar between variant and non-variant heterozygotes. For diagnoses for which stage distribution was unavailable in SEER, we used the proportion with resectable disease for choroid plexus (based on expert opinion) or low/intermediate disease medulloblastoma as a proxy for disease extent.[29] Treatment by stage for each diagnosis was based on expert opinion and standard care. Except for osteosarcoma, all cancers diagnosed as advanced disease were assumed to require radiation; in addition, all medulloblastoma and rhabdoid tumors received radiotherapy as frontline therapy (in addition to chemotherapy).

Mortality data

Cancer-specific mortality risks were based on 5-year cause-specific estimates in SEER[3]. We assumed that at 5-years post-diagnosis, cancer mortality risk was negligible. Background mortality rates were based on US cohort life tables.[30,31] Individuals who received chemotherapy and/or radiation as part of cancer treatment faced excess late mortality risks as adults starting at age 20.[32,33] Excess mortality rates were based on the Childhood Cancer Survivors Study participants diagnosed between 1970 and 1999.[34] As estimates beyond the initial decades following cancer diagnosis are not yet available, we assumed rates beyond age 65 remained constant at levels observed between ages 55 and 64.

Cost data

Costs, shown in **Supplemental Table 5**, were based on published literature and national databases. For cancer treatment, we based costs from a population-based analysis of cancer resource use;[35] we assumed that all cancers incurred initial/continuing care costs at diagnosis, while only cancers that resulted in death incurred final care costs. For thyroidectomy, primary prevention for *RET* heterozygotes, cost was based on a cross-sectional analysis of Healthcare Cost and Utilization Project Nationwide Inpatient data.[36] For surveillance care, we assumed that all variant heterozygotes would have an annual physician visit, and undergo recommended procedures as summarized in **Table 1**. We used 2018 Medicare reimbursement rates as a proxy for costs.[37] For t-NGS, we assumed a cost of $55 for the 11-gene panel test (i.e. $5 per gene) based upon expert input, current cost of newborn screening (NBS) and commercial cost for a panel test (Invitae Pediatric Solid Tumors Panel).[38] We assumed that this cost reflected the incremental cost of adding the panel to a newborn screening program with established infrastructure for genetic screening. Patient time costs were based on parental time lost from work and the 2018 median hourly wage.[39] We assumed that 1) parents would miss half a day of work for each surveillance test or physician visit and 2 weeks for thyroidectomy and 2) approximately one-third of children diagnosed with cancer would have one parent who would stop working during cancer treatment (2 months for surgery, 6 months for chemotherapy and 1 year for radiotherapy).[40-42] Costs reported in Canadian dollars were converted to US dollars using the CAD-US exchange rate as of 07/01/2018. All costs were inflated to 2018 U.S. dollars using the Consumer Price Index.

Cost-effectiveness analysis

The economic evaluation of t-NGS compared to Usual Care was conducted from a modified societal perspective following established recommendations.[43,44] All costs and life years were discounted at 3% per year. We calculated an incremental cost-effectiveness ratio (ICER), defined as the additional cost of t-NGS divided by its additional clinical benefit compared to Usual Care, and expressed as cost per life year (LY) gained. ICERs were calculated as the ratio of the mean-costs divided by the mean-effects among the 1000 simulations.

Compared to Usual Care, the ICER for t-NGS was $244,860 per LY gained (95% UI, $181,500 to $327,520). Results were most sensitive to P/LP variant prevalence among cancer cases and 5-year survival rates for localized and advanced disease, moderately sensitive to the proportion of cancers diagnosed as advanced disease and the P/LP variant prevalence among controls, and robust to assumptions on surveillance and cancer treatment costs and excess mortality risks associated with cancer treatment (**Supplemental Figure 2**).

The study's Impact Inventory List is provided in **Supplemental Table 6**.

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Supplemental Table 1. Model parameters: Counts of 2-star[a] pathogenic (P)/likely pathogenic (LP) variants by source

Gene	Variants identified in ClinVar	Variants confirmed by LMM	Variants confirmed by LMM with entries in gnomAD[b]
ALK	0	0	0
PHOX2B	0	0	0
APC	195	191	7
DICER1	68	67	4
RB1	35	35	2
RET	30	30	1[c]
SMARCB1	5	4	0
SUFU	2	2	0
PTCH1	21	18	0
TP53	116	111	16
WT1	5	5	0
Total	477	463	30

[a] At least 2-star submitter in ClinVar.

[b] For genes without any P/LP variants reported in gnomAD, we assumed an allele frequency of 0.5 among the 282,912 alleles in gnomAD**.**

[c] Excludes 12 RET P/LP variants not located in exon 17 (codon M918T) and exon 15 (codon A883F).

Supplemental Table 2. Additional details on variants in Supplemental Table 1

Variant Name (Transcript and DNA change)	Chromosome	Genomic Position Start	Genomic Position End	Reference Allele	Alternative Allele	Gene	Exon Number	Intron Number	Amino Acid Change	Amino Acid Change Type	Classification	Allele Frequency
NM_000038.4:c.70C>T	5	112090657	112090657	C	T	APC	2		p.Arg24X	Nonsense/ stop gain	Pathogenic	2.38815E-05
NM_000038.4:c.221-2A>G	5	112102884	112102884	A	G	APC	4	3	NA	NA	Likely Pathogenic	3.98222E-06
NM_000038.4:c.288T>A	5	112102953	112102953	T	A	APC	4		p.Tyr96X	Nonsense/ stop gain	Pathogenic	3.97665E-06
NM_000038.4:c.646C>T	5	112128143	112128143	C	T	APC	7		p.Arg216X	Nonsense/ stop gain	Pathogenic	3.9976E-06
NM_000038.4:c.3183_3187delACAAA	5	112174471	112174475	TAAAAC	T	APC	16		p.Gln1062X	Nonsense/ stop gain	Pathogenic	3.99218E-06
NM_000038.4:c.3927_3931delAAAGA	5	112175212	112175216	TAAAAG	T	APC	16		p.Glu1309AspfsX4	Frameshift/ frameshift,	Pathogenic	7.96686E-06
NM_000038.4:c.4669_4670delAT	5	112175959	112175960	CTA	C	APC	16		p.Ile1557X	Nonsense/ stop gain	Pathogenic	3.99869E-06
NM_030621.3:c.3007C>T	14	95572101	95572101	G	A	DICER1	21		p.Arg1003X	Nonsense/ stop gain	Likely Pathogenic	3.97975E-06
NM_030621.3:c.2888_2889delCT	14	95572476	95572477	CAG	C	DICER1	20		p.Pro963ArgfsX3	Frameshift/ frameshift	Pathogenic	3.9781E-06
NM_030621.3:c.1966C>T	14	95579503	95579503	G	A	DICER1	14		p.Arg656X	Nonsense/ stop gain	Pathogenic	3.9781E-06
NM_030621.3:c.1870C>T	14	95582041	95582041	G	A	DICER1	13		p.Arg624X	Nonsense/ stop gain	Pathogenic	3.97678E-06
NM_000321.2:c.1333C>T	13	48953730	48953730	C	T	RB1	14		p.Arg445X	Nonsense/ stop gain	Pathogenic	4.01745E-06
NM_000321.2:c.1981C>T	13	49033844	49033844	C	T	RB1	20		p.Arg661Trp	Missense/ missense	Pathogenic	1.59157E-05
NM_020630.4:c.2753T>C	10	43617416	43617416	T	C	RET	16		p.Met918Thr	Missense/ missense	Pathogenic	3.97649E-06
NM_000546.5:c.1010G>A	17	7574017	7574017	C	T	TP53	10		p.Arg337His	Missense/ missense	Pathogenic	1.19595E-05
NM_000546.5:c.844C>T	17	7577094	7577094	G	A	TP53	8		p.Arg282Trp	Missense/ missense	Pathogenic	3.97757E-06
NM_000546.5:c.818G>T	17	7577120	7577120	C	A	TP53	8		p.Arg273Leu	Missense/ missense	Pathogenic	3.98321E-06
NM_000546.4:c.818G>A	17	7577120	7577120	C	T	TP53	8		p.Arg273His	Missense/ missense	Pathogenic	1.59328E-05
NM_000546.5:c.817C>T	17	7577121	7577121	G	A	TP53	8		p.Arg273Cys	Missense/ missense	Pathogenic	1.19593E-05
NM_000546.5:c.743G>A	17	7577538	7577538	C	T	TP53	7		p.Arg248Gln	Missense/ missense	Pathogenic	1.19297E-05
NM_000546.5:c.742C>T	17	7577539	7577539	G	A	TP53	7		p.Arg248Trp	Missense/ missense	Pathogenic	3.97652E-06

NM_000546.5:c.734G>A	17	7577547	7577547	C	T	TP53	7		p.Gly245Asp	Missense/ missense	Pathogenic	3.97671E-06
NM_000546.5:c.722C>T	17	7577559	7577559	G	A	TP53	7		p.Ser241Phe	Missense/ missense	Pathogenic	3.97652E-06
NM_000546.5:c.659A>G	17	7578190	7578190	T	C	TP53	6		p.Tyr220Cys	Missense/ missense	Pathogenic	7.9552E-06
NM_000546.5:c.638G>A	17	7578211	7578211	C	T	TP53	6		p.Arg213Gln	Missense/ missense	Pathogenic	3.97674E-06
NM_000546.5:c.586C>T	17	7578263	7578263	G	A	TP53	6		p.Arg196X	Nonsense/ stop gain	Pathogenic	3.97655E-06
NM_000546.5:c.542G>A	17	7578388	7578388	C	T	TP53	5		p.Arg181His	Missense/ missense	Likely Pathogenic	1.19368E-05
NM_000546.5:c.524G>A	17	7578406	7578406	C	T	TP53	5		p.Arg175His	Missense/ missense	Pathogenic	3.97969E-06
NM_000546.5:c.473G>A	17	7578457	7578457	C	T	TP53	5		p.Arg158His	Missense/ missense	Pathogenic	3.97981E-06
NM_000546.5:c.455C>T	17	7578475	7578475	G	A	TP53	5		p.Pro152Leu	Missense/ missense	Pathogenic	7.95944E-06

Supplemental Table 3. Model parameters: Prevalence of P/LP variants among cancer cases and controls

Gene	Cancer	Prevalence of P/LP variants, mean (range)	
		Among pediatric cancer cases[16-28]	Among controls[2]
ALK	Neuroblastoma	0.033 (0.010-0.143)	0.000004 (0-0.000037)
PHOX2B		0.001 (0-0.005)	0.000003 (0-0.000029)
APC	Hepatoblastoma	0.101 (0.002-0.354)	0.000095 (0.000036-0.000179)
DICER1	Pleuropulmonary blastoma	0.778 (0.403-0.981)	0.000024 (0.000001-0.000080)
RB1	Retinoblastoma	0.921 (0.813-0.975)	0.000008 (0-0.000069)
RET	Medullary thyroid carcinoma	0.948 (0.829-0.996)	0.000008 (0-0.000068)
SMARCB1	Rhabdoid tumor	0.350 (0.216-0.511)	0.000004 (0-0.000038)
SUFU	Medulloblastoma	0.199 (0.105-0. 312)	0.000003 (0-0.000045)
PTCH1		0.198 (0.101-0.310)	0.000003 (0-0.000039)
TP53	Adrenocortical carcinoma	0.501 (0.346-0.661)	0.000206 (0.000087-0.000353)
	Choroid Plexus	0.441 (0.126-0.805)	
	Osteosarcoma	0.040 (0.141-0.075)	
	Rhabdomyosarcoma	0.238 (0.112-0.671)	
WT1	Wilms tumor	0.022 (0.004-0.056)	0.000004 (0-0.000038)

Supplemental Table 4. Model parameters: Cancer data

Cancer (ICD-O-3 code)	Cancer cases before age 20 among a 3.7M birth cohort[a], mean (range)	Proportion diagnosed at advanced disease[b], mean (range)	Proportion 5-year survival rate[c]		Cancer treatment regimen[d]	
			Localized, mean (range)	Advanced, mean (range)	Localized	Advanced disease
Neuroblastoma (9490, 9500)	481.9 (446.5-517.3)	0.792 (0.759-0.824)	0.977 (0.953-1)	0.758 (0.732-0.786)	Observation, Surgery or Chemotherapy	Surgery, RT, Chemotherapy
Hepatoblastoma (8970)	109.0 (95.6-126.1)	0.557 (0.488-0.617)	0.904 (0.858-0.956)	0.728 (0.678-0.785)	Surgery, Chemotherapy	Surgery, RT, Chemotherapy
Pleuropulmonary blastoma (8973)	8.3 (4.6-16.1)	0.583 (0.305-0.784)	1 (1-1)	0.561 (0.396-0.766)	Surgery	Surgery, RT, Chemotherapy
Bilateral retinoblastoma (9510-9514)	74.5 (62.6-89.0)	0.283 (0.244-0.325)	0.9930 (0.983-1)	0.942 (0.898-0.997)	Local chemotherapy or Surgery	Surgery, RT, Chemotherapy
Medullary thyroid carcinoma (8345, 8510)	8.8 (5.9-14.5)	0.375 (0.222-0.522)	1 (1-1)	0.734 (0.570-0.941)	Surgery	Surgery, RT, Chemotherapy
Rhabdoid tumors (8963, 9508)	72.0 (59.9-86.7)	0.925 (0.876-0.962)	0.677 (0.509-0.870)	0.347 (0.319-0.374)	Surgery, RT, Chemotherapy	Surgery, RT, Chemotherapy
Medulloblastoma[e] (9470-9471)	97.4 (83.2-119.8)	0.321 (0.259-0.395)	0.801 (0.745-0.882)	0.304 (0.283-0.334)	Surgery, RT, Chemotherapy	Surgery, RT, Chemotherapy
Adrenocortical carcinoma (8370-8375)	17.3 (12.9-23.7)	0.631 (0.327-0.903)	1 (1-1)	0.291 (0.200-0.417)	Surgery	Surgery, RT, Chemotherapy
Choroid Plexus (9390)	16.7 (12.0-22.9)	0.250 (0.108-0.402)	0.701 (0.579-0.849)	0.304 (0.251-0.367)	Surgery	Surgery, RT, Chemotherapy
Osteosarcoma (9180-9187, 9191-9195, 9200)	400.6 (375.1-431.8)	0.667 (0.635-0.707)	0.840 (0.799-0.882)	0.617 (0.589-0.647)	Surgery, Chemotherapy	Surgery, Chemotherapy
Rhabdomyosarcoma[e] (8900-8905, 8910, 8912, 8920, 8991)	134.5 (119.8-156.2)	0.679 (0.639-0.715)	0.885 (0.845-0.944)	0.551 (0.525-0.590)	Surgery, Chemotherapy	Surgery, RT, Chemotherapy
Wilms tumor (8959, 8960)	397.2 (361.4-430)	0.570 (0.535-0.606)	0.974 (0.955-0.993)	0.889 (0.860-0.918)	Surgery, Chemotherapy	Surgery, RT, Chemotherapy

RT, radiotherapy

[a] Based on age-specific SEER incidence rates between ages 0 and 19 for all cancers, except for medulloblastoma and rhabdomyosarcoma (between ages 0 and 5) and medullary thyroid carcinoma (between ages 0 and 10). Assumed 40% of retinoblastoma was bilateral.

[b] Advanced disease defined as regional, distant and unstaged tumors. Choroid plexus based on expert opinion. Medulloblastoma advanced disease defined as non-resectable.

[c] Based on SEER, except for choroid plexus and medulloblastoma which were based on expert opinion.

[d] Based on expert opinion. Assumed localized tumors treated with surgery faced negligible excess late mortality risks. Non-late effect chemotherapy for localized retinoblastoma and neuroblastoma.

[e] P/LP variants associated with cancer cases diagnosed before age 5 only.

Supplemental Table 5. Model parameters: Cancer treatment and surveillance costs

Type	Description	Costs (2018$)	Reference
Cancer treatment costs			
	Initial/continuing phase[a]	$170,000	[35]
	Final phase[b]	$365,000	
Prophylactic treatment			
	Thyroidectomy	$16,620	[36]
Surveillance visits and procedures (CPT code)			
	Physician visit (99213)	$188	[37]
	Eye exam (92014)	$195	
	Brain MRI (70553)	$842	
	Abdominal US (76700)	$240	
	Chest x-ray (71048)	$157	
	Chest CT (71270)	$493	
	Moderate sedation (99155)	$99	

CPT, Current Procedural Terminology

[a] Incurred at cancer diagnosis

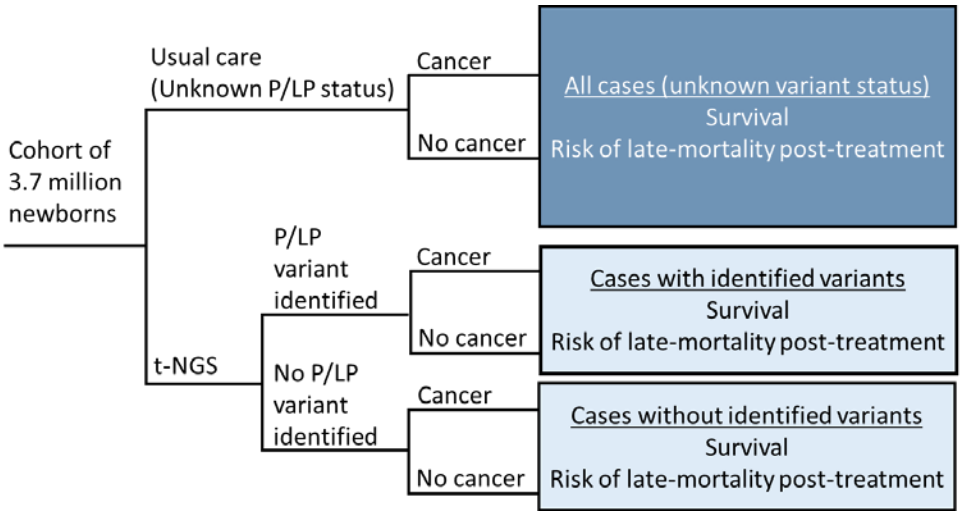
[b] Incurred at cancer death

Supplemental Table 6. Recommendations from the Second Panel on Cost-Effectiveness in Health and Medicine – Impact Inventory List

Sector	Type of Impact	Included in This Reference Case Analysis From … Perspective		Notes on Sources of Evidence
		Health Care Sector	Societal	
Formal Health Care Sector				
Health	Health outcomes (effects)			
	Longevity effects		√	Simulation models, published studies, expert opinion
	Health-related quality-of-life Effects			
	Other health effects		√	Childhood Cancer Survivor Study data, expert opinion
	Medical costs			
	Paid for by third-party-payers		√	Medicare reimbursement rates, published studies
	Paid for by patients out-of-pocket			
	Future related medical costs (payers and patients)			
	Future unrelated medical costs (payers and patients)			
Informal Health Care Sector				
Health	Patient-time costs	N/A	√	Published studies, Bureau of Labor Statistics
	Unpaid caregiver-time costs	N/A		
	Transportation costs	N/A		
Non-Health Care Sectors (with examples of possible items)				
Productivity	Labor market earnings lost	N/A		
	Cost of unpaid lost productivity due to illness	N/A		
	Cost of uncompensated household production	N/A		
Consumption	Future consumption unrelated to health	N/A		
Social Services	Cost of social services as part of interventions	N/A		
Legal or Criminal Justice	Number of crimes related to interventions	N/A		
	Cost of crimes related to interventions	N/A		

Education	Impact of intervention on educational achievement of population	N/A
Housing	Cost of intervention on home improvements (e.g., removing lead paint)	N/A
Environment	Production of toxic waste pollution by intervention	N/A
Other (specify)	Other impacts	N/A

Supplemental Figure 1. Model overview: Comparison of t-NGS and Usual care. Given the goals of newborn screening (NBS), which is focused on improving child health, the model focuses on early onset of pediatric malignancies. All newborns are at risk for developing cancer before age 20. Upon diagnosis of a cancer, survival is based on stage at diagnosis. Individuals who survive cancer face treatment-related late mortality risks as adults. Under Usual Care, the presence of a pathogenic (P)/likely pathogenic (LP) variant is unknown. Under t-NGS, all newborns undergo genetic screening with the 11-gene panel. Newborns with P/LP variants identified via genetic screening undergo recommended cancer surveillance for the variant identified. In this scenario, we assumed that cancer cases are detected earlier and diagnosed as localized disease, with more favorable survival rates and lower treatment-related late mortality risks.



Supplemental Figure 2. Sensitivity analysis on ICER for t-NGS: Tornado diagram (with cost of 11-gene panel = $55). Based on one-way sensitivity analyses, this figure depicts the relative influence of select model parameters on results for t-NGS. The x-axis shows the effect of changes in selected variables on the ICER for t-NGS (compared to Usual Care). The y-axis shows selected model parameters, with the base case value and range used in the sensitivity analysis shown in parentheses. The shaded bars indicate the variation in the ICER associated with changes in the value of the indicated variable while all other variables were held constant. The dotted vertical black line indicates the ICER for the base case. ICERs were calculated as the ratio of the mean-costs divided by the mean-effects among the 1000 simulations.