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

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Abstract

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 vs. usual care. Using data from clinical studies, ClinVar and gnomAD, the presence of pathogenic/likely pathogenic variants in *RET, RB1, TP53, DICER1, SUFU, PTCH1, SMARCB1, WT1, APC, ALK, PHO2XB* 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, 1803 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

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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.

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 U.S. 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 non-cancer 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 Figure 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.

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 1000 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*), nor 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 "non-penetrant 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 to Usual Care, expressed as cost per life year (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 life year (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 non-cancer 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 1803 individuals would develop a CPS-associated cancer before age 20 (95% UI, 1756 to 1850), 13.3% of whom would have P/LP CPS variants (95% UI, 11.3% to 15.7%). Under t-NGS, 1584 individuals with P/LP CPS variants (95% UI, 1230 to 2026) would be identified, 232 (95% UI, 196 to 278) of whom would develop cancer before age 20 (i.e., PVS) and 1353 (95% UI, 991 to 1788) 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 to 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 2937 (95% UI, 2244 to 3879) life-years. The estimated benefit for all outcomes was considerably higher among individuals with P/LP variants (Figure 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 to 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 vs. 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 Figure 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 1580 individuals with P/LP CPS variants among 3.7 million newborns each year in the US. 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 upon genetic testing decreased anxiety and did not create an excessive burden.[24]

We assumed full adherence to surveillance recommendations to estimate of 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 NCI Childhood Cancer Data Initiative aims to collect data on every child diagnosed with cancer in the US 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 which 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY STATEMENT

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 are also provided in Supplemental Table 2.

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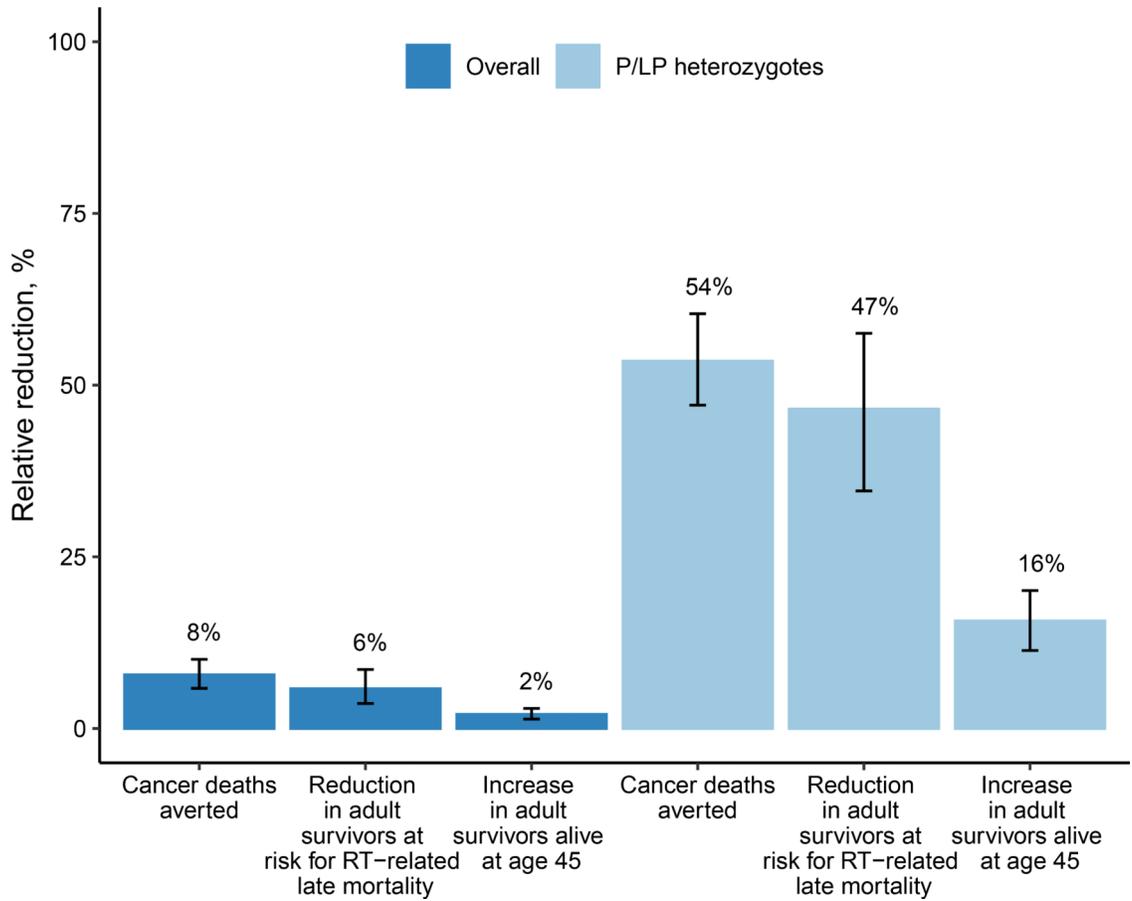
Figure 1. Modeled clinical outcomes for t-NGS vs. Usual Care.
Shown are estimates for the overall cohort of 3.7 million screened newborns and among the subset of newborns with identified P/LP variants. Bars indicate the 95% uncertainty intervals among the 1000 simulations.

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	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
	Choroid Plexus			
	Rhabdomyosarcoma			
	Osteosarcoma			
SMARCB1	Rhabdoid Tumors	Stage shift, increased survival (these are only curable if fully resected)	Ultrasound 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 y, 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

[a] Recommended routine surveillance also serial ultrasounds and biochemical monitoring of serum calcitonin levels for early detection of later-onset tumors (not modeled).

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					Cancer deaths		5-year survivors at risk for radiation-related late mortality		5-year survivors alive at age 45	
	Penetrant variant status, n	Non-penetrant variant status, n	Individuals without P/LP variants who develop cancer before age 20, n	Penetrance by age 20, %	Relative risk (RR) of cancer before age 20 among individuals with P/LP variants[c]	Usual Care	% change with t-NGS	Usual Care	% change with t-NGS	Usual Care	% change 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)	1254 (1215–1292)	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)

[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 to individuals without P/LP variants.