HEALTH PARTNERS
CONSULTING GROUP LIMITED

Cost-effectiveness of newborn screening for Severe Combined Immune Deficiency

A report prepared for the National Screening Unit

March 2014

TOMORROW'S HEALTH TODAY

Disclaimer

While all reasonable care has been taken to ensure that information contained in this document is true and accurate at the time of writing, changes in circumstances after the time of publication may impact on the accuracy of its information. Data has been obtained from health services and used in good faith. Health Partners Consulting Group accepts no liability for any errors in the data supplied, or any action taken or not taken as a result.

Lead authors for Health Partners Consulting Group:
Dr Gary Jackson
Luke Williams
Contact: gary@healthpartnersconsulting.com
www.healthpartnersconsulting.com

Suggested citation.

Health Partners Consulting Group (2014). Cost-effectiveness of newborn screening for Severe Combined Immune Deficiency. A Report prepared for the National Screening Unit.

Acknowledgements

Our thanks to the external reviewer, health economist Dr Richard Edlin of the School of Population Health, University of Auckland, whose many suggestions assisted in improving the robustness of the modelling.

Our thanks also to Nigel Atherfold, Director, TDB Advisory, who provided many valuable contributions as member of the project team.

Contents

Executive summary

Severe Combined Immune Deficiency (SCID) is a life-threatening disease of infants caused by genetic defects that prevent the normal development of T-cells. It affects children in the first year of life. If left untreated, the infections are universally fatal, usually in the first year of life. Evidence suggests that early detection of SCID is associated with improved treatment outcomes and lower health system costs.

Over the past several years, a number of US States and Districts have been piloting newborn screening for SCID using a dried blood spot assay test. Early evidence suggests that the screening test is efficacious, with no known cases of SCID being undiagnosed.

US data suggests a prevalence rate of SCID (in its 'classical' form) of around 1 in 69,000 births, but a wide range of incidence rates has been reported at State and Territories levels. A SCID prevalence rate in New Zealand has not been previously estimated. However, in a review carried out for this work, over the past 13 years there have been eight identified cases of SCID in New Zealand, suggesting an incidence rate of around 1 in 104,000 births (see Appendix 1).

The National Screening Unit (NSU) is considering conducting testing for SCID in New Zealand as part of the Newborn Metabolic Screening Programme (NMSP), modelled on the testing methodology used in the US pilots. As part of the NSU's decision-making process regarding introduction of new screening regimes, a cost-effectiveness assessment of the regime is required. The NSU commissioned Health Partners to undertake the cost-effectiveness analysis of conducting newborn screening for SCID in New Zealand. Specifically, the NSU requested:

- An estimate of the incremental cost-effectiveness per life-year gained if newborn testing were introduced
- Analysis of the sensitivity of key variables driving the estimate of incremental cost-effectiveness.

The analytical objective is to answer the following question:

> *Would adding newborn screening for SCID to the National Newborn Metabolic Screening Programme be a cost-effective alternative in terms of public health system funding and life-years saved to the current regime of opportunistic clinical diagnosis?*

The analysis concentrates on so-called classical SCID.

In December 2013, Health Partners provided the NSU with an assessment of the international evidence regarding the potential economic impact of newborn screening for SCID. The assessment distilled the key parameters shaping the potential economic impact of newborn screening for SCID, with these being:

- Number of births per year
- Incidence of SCID
- Early opportunistic diagnosis resulting from family history
- Efficacy of testing regimes for SCID specifically in regard to quantitative polymerase chain reaction for T-cell receptor excision circles (TRECs) as used in the US pilots
- The costs associated with a newborn screening regime including initial screening costs and confirmatory testing, particularly in regard to false positives
- SCID treatment options, the timing of diagnosis and treatment, and the effectiveness of treatment options
- Post-treatment support requirements and associated costs
- Public health system costs associated with cases of SCID.

These parameters form the basis for cost-effectiveness modelling, with base-case values assigned to each parameter (see Table 4).

Base-case assumptions suggest that on average the New Zealand public health system currently spends approximately $157k per year on SCID diagnosis and treatment for a gain of 4.1 life-years (see Table 1)Table 6 : - that is, with no screening, and relying on opportunistic clinical diagnosis. Based on the same set of assumptions, adding newborn screening for SCID to the NMSP may result in saving of 10.0 life years at a cost of $30k per life-year. Individuals found by screening compared with those discovered after infections have occurred are significantly more likely to survive their illness, have better outcomes, and cost the public health system less to treat.

We estimate that the total cost of adding newborn screening for SCID to the NMSP, inclusive of treatment costs, would be around $460k per year. The net cost impact to the public health system would be around $303k per year.

Table 1 : Base-case estimate of the cost-effectiveness of adding newborn screening for SCID to the NMSP

Results	Costs	Life-years	Cost/LY
No screening	$157,092	4.1	
Screening	$460,166	14.0	
Net impact	$303,073	10.0	$30,409
ICER (cost per life-year gained)			$30,409

Our base-case assumption based on New Zealand experience is that an infant with SCID who does not receive an HSCT has an average life expectancy of ~1 year. We assume that life expectancy of children with SCID who do receive an HSCT is influenced by whether their condition has been diagnosed and treated early or late, and whether they require post-treatment support (mainly Intravenous immunoglobulin (IVIG)[1]). Based on these assumptions we estimate the following per SCID case (undiscounted) life-year scenarios:

1. No screening, no treatment – life expectancy 1 year, life years gained 0;
2. No screening, late treatment – life expectancy 36-42 years, life years gained 35-41 years;
3. Screening, early treatment – life expectancy 61-72 years, life years gained 60-71 years.

There is considerable uncertainty regarding the New Zealand incidence rate of SCID, and the long-term effectiveness of treatment for SCID. In light of this, we have conducted univariate sensitivity analysis of key model parameters: incidence rate, survival outcomes and treatment costs associated with early and late detection, as shown in Table 2.

Table 2 : Summary of sensitivity analysis by key parameters (other parameters base-case)

Parameter	ICER range	Additional comment
Incidence rate	$8k - $30k	If there were no cases of SCID in a given year, the cost to the public health system of a screening programme would equate to $325k
Life expectancy	$30k - $197k	Range from estimated base-case life expectancy of SCID cases following HSCT ($30k) and 5-year survival only ($197k)
HSCT treatment cost	$29k - $32K	Estimated standard error of early and late detection. HSCT added to base-case cost
Discount rate scenarios	$11k- $41k	Adjustment of discount rate from 0-5% (3.5% base-case)

[1] If the transplant is not completely successful additional immunoglobulin support may be required. This usually takes the form of 4-weekly Intravenous immunoglobulin (IVIG).

Public health system funding and prioritisation decisions are not formally based on pre-determined willingness to pay thresholds per life years gained. However, for indicative purposes we have assessed the SCID incidence rate and TREC assay cost per test respectively required to meet indicative willingness to pay thresholds (see Table 3).

Table 3 : Willingness-to-pay thresh-holds per life-year gained based on alternative incidence scenarios and cost per screening test

Willingness-to-pay thresholds	$5,000 per LY	$15,000 per LY	$30,000 per LY	$50,000 per LY
Incidence (other parameters base-case)	1:23,250	1:55,100	1:102,900	1:166,650
TREC Assay cost (base-case incidence)	$0.97	$2.64	$5.15	$8.49

We conclude that based on the evidence of screening for SCID in the US, with the assumptions we have derived from the international literature, current prevalence and costs in the New Zealand system, and clinical expert estimates, the cost-effectiveness of adding screening for SCID to the New Zealand newborn metabolic screening programme would appear to be in line with existing heath care interventions, at an estimated cost of $30k per life year. If, as expected, the incidence rate is higher than that estimated based on current cases, the estimated costs per life year would decrease, potentially significantly. However, we note that there are some significant uncertainties related to the long-term effectiveness of treatment for SCID, which if different to our base-case assumptions, would materially impact on our estimate of screening programme cost-effectiveness. We also note the current costs of care are based on a small number of cases (8), and hence uncertainty remains around the cost estimates.

Purpose

This report provides an economic analysis of the potential cost-effectiveness of conducting testing for Severe Combined Immune Deficiency (SCID) in New Zealand as part of the Newborn Metabolic Screening Programme (NMSP). Specifically, it provides:

- An estimate of the incremental cost-effectiveness per life-year gained if newborn testing were introduced
- Analysis of the sensitivity of key variables driving the estimate of incremental cost-effectiveness.

A companion document *Screening for SCID - Literature Review* (Health Partners Consulting Group, December 2013) outlines the data sources in more detail.

Background

SCID is a life-threatening disease of infants caused by genetic defects that prevent the normal development of T-cells. It affects children in the first year of life. Most children with SCID are not diagnosed until 6-9 months of age, when the onset of severe infections occurs due to their underdeveloped immune systems. If left untreated, the infections are universally fatal, usually in the first year of life. Treatment is possible and potentially curative through haematopoietic stem cell transplant (HSCT), but has poor outcomes once severe infections have occurred. Early diagnosis and HSCT treatment in the first few months of life, before significant infections occur, can markedly improve outcomes.

Since 2010, a number of US States and Territories have piloted SCID screening for all newborns. The US experience suggests that testing for SCID is efficacious in detecting the disorder (as well as some other immune disorders) and enables earlier treatment intervention. US data also suggests that the costs of treating a child with SCID older than 3.5 months is approximately four times greater than under 3.5 months (Buckley, 2012).

US data suggests a prevalence rate of SCID of around 1 in 69,000 births but a wide range of incidence rates has been reported at State and Territory levels. A SCID prevalence rate in New Zealand has not been estimated previously. However, a review carried out for this project shows that over the past 13 years there have been eight identified cases of SCID in New Zealand, suggesting an incidence rate of around 1 in 104,000 births (see Appendix 1). This suggests that on average there will be less than one case per year, and that in some years there will be no cases of SCID. However, it is likely that some cases of SCID have gone undetected in New Zealand over the past 13 years – the affected cases dying of infection without being diagnosed. If a screening programme was to be instituted, it is likely the true rate would be somewhat higher than these past figures would indicate.

The National Screening Unit ('NSU') is currently considering a proposal to add testing for SCID to the NMSP. To inform its consideration, the NSU requires an assessment of the cost-effectiveness of doing so. Specifically, the NSU requires:

- Assessment of the evidence of the economic impact of newborn screening for SCID in overseas jurisdictions
- An estimate of the incremental cost-effectiveness per life-year saved if newborn testing were to be introduced
- Analysis of the sensitivity of key variables driving the estimate of incremental cost-effectiveness.

In December 2013, Health Partners Consulting Group ('Health Partners') provided the NSU with an assessment of the international evidence regarding the potential economic impact of newborn screening for SCID. The assessment distilled the key parameters shaping this potential economic impact, with these being:

- Number of births per year

- Incidence of SCID
- Early opportunistic diagnosis resulting from family history
- Efficacy of testing regimes for SCID specifically in regard to quantitative polymerase chain reaction for T-cell receptor excision circles (TRECs) as used in the US pilots
- The costs associated with a newborn screening regime, including initial screening costs and confirmatory testing particularly in regard to false positives
- SCID treatment options, the timing of diagnosis and treatment, and the effectiveness of treatment options
- Post-treatment support requirements and associated costs
- Public health system costs associated with cases of SCID.

These parameters form the basis for cost-effectiveness modelling, with base-case values assigned to each parameter.

Analytical scope and objective

As agreed with the NSU, the analytical perspective of the economic analysis of adding newborn screening for SCID to the NMSP is that of a public health funder – that is, only costs borne by the health system, such as hospitalisations, are included. Costs borne by parents such as travel expenses or loss of earnings, or by employers such as sick leave, are not included. The rationale for adopting a public health funder perspective is:

- The decision to implement (or not) newborn screening for SCID will have an impact on Vote Health (public health funding) and direct patient healthcare costs, and hence these costs need to be included in the analysis
- Vote Health is separate from other public sector budgets; hence any patient benefits and/or costs that accrue beyond individual health outcomes are outside the scope of the NSU's or Ministry of Health's control
- This approach accords with other stated economic analysis perspectives undertaken in the New Zealand public health system - for example, by PHARMAC and the National Health Committee (NHC). Adopting a similar approach will enable prioritisation trade-offs between alternative public health system investment options.

The analytical objective is therefore to answer the following question:

> *Would adding newborn screening for SCID to the National Newborn Metabolic Screening Programme be a cost-effective alternative in terms of public health system funding and life-years saved to the current regime of opportunistic clinical diagnosis?*

The analysis concentrates on so-called 'classical SCID'. The screening programme will identify other immunodeficiency and variant syndromes (eg, the Californian programme found one 'variant' SCID for each case of classical SCID, and a further 0.6 other syndrome patients). However, these other cases are a mixture of individually rare conditions, each with different prognostic and treatment possibilities. It proved difficult to assess the potential costs that might be incurred and benefits that might accrue to these children given the screening experience to date internationally. This cost-effectiveness analysis is thus based solely on the detection of classical SCID.

The original intention had been to use a quality-adjusted life year (QALY) approach to valuing outcomes. However, several factors led to the conclusion that a straight-forward life-years approach would be more appropriate:

- There were no measured QALY values for SCID cases, nor for post-transplant survivors

- Even the imputation of the likely life expectancy required specific assumptions to be made
- the most likely outcome expected of an early-detected successful transplant is a full life with no health impact (ie, 1 life-year = 1 QALY), so little effect would be expected
- Critique in the literature of attempts to estimate QALYs (Grosse 2012).

The effect of not including QALYs is likely to be slightly conservative in that transplants in late-detected cases are more likely to have adverse outcomes. We could speculate that the resulting life-years might be less than 1:1 with QALYs, so the approach taken may slightly favour the no screening option.

Methodology

We have used a decision tree modelling approach to assess the potential cost-effectiveness of adding newborn screening for SCID to the NMSP. We have selected this approach instead of others like Markov modelling since:

- Interaction between individuals is not important in the incidence of SCID
- SCID generally progresses in a linear way, with efficacious treatment being live saving
- Meaningful clinical and financial events generally occur within the first year of a child's life
- The decision tree approach balances simplicity with accuracy, with uncertainty accommodated through sensitivity analysis.

The decision tree includes two main branches: a no screening option (current regime of opportunistic diagnosis) and a screening option (all newborns being screened for SCID using the TREC assay methodology as per US pilots). The no screening and screening branches then both fork between early and late detection of SCID. The screening option includes an additional branch for false positive and true negative screening outcomes.

A hypothetical cohort of children move through the decision tree based on pre-determined transition probabilities. The hypothetical cohort of children is based on the average number of children born in New Zealand each year since 1999 – 59,431 children.

Table 4 provides a detailed breakdown of our base-case assumptions based on the earlier literature review. The following paragraphs provide further information on the key parameter areas driving the decision tree model: transition probabilities, costs and outcomes. Figure 3 provides the decision tree for the base-case model.

Table 4 : Base-case model assumptions

Assumption	Value	Discounted - NPV	Comment
Births and SCID incidence			
Number of births	59,431		Statistics NZ - average birth-rate since 1999
SCID incidence (number of births per case of SCID)	104,215		Based on 8 confirmed cases 2000-2013
Transition probabilities – 'no screening' & 'screening' options			
Probability - early detection - family history	0.10		Mean of NZ rate (0%) & international literature estimate (20%)
Probability - early detection – undergoing HSCT	0.95		Estimated 5% other co-existing conditions ruling out HSCT - clinical expert estimate
Probability - early detection - successful HSCT	0.90		10% of early HSCT need further intervention. Clinical expert estimate
Probability - early detection - successful HSCT - Post-treatment support (PTS)	0.10		International literature cites ~12% of HSCT patients
Probability - early detection - successful HSCT - No PTS	0.88		As above
Probability - early detection - successful HSCT – Death	0.02		Estimated from Buckley (2011)
Probability - early detection - Unsuccessful HSCT - subsequent HSCT	0.90		Clinical expert estimate
Probability - early detection - Unsuccessful HSCT - successful subsequent HSCT	0.90		Clinical expert estimate
Probability - early detection - Unsuccessful HSCT – unsuccessful subsequent HSCT	0.10		Assume death most likely outcome at that point
Probability - early detection - unsuccessful HSCT - subsequent HSCT – PTS	0.20		Estimated from Railey (2009), Patel (2009)
Probability - early detection - unsuccessful HSCT - successful subsequent HSCT - No PTS	0.75		As above
Probability - early detection - successful subsequent HSCT – Death	0.05		Estimated from Buckley (2011)
Probability - late detection – receiving HSCT	0.25		NZ rate - 2 cases of 8 received HSCT
Probability - late detection - successful HSCT	0.71		Estimated from Buckley (2011). Note NZ rate - 1 case of 2
Probability - late detection - successful HSCT – PTS	0.30		Estimated from Railey (2009), Patel (2009)
Probability - late detection - Successful HSCT - No PTS	0.60		As above
Probability - late detection - unsuccessful HSCT - subsequent HSCT	0.90		Clinical expert estimate. Note NZ rate - 1 case of 2
Probability - late detection - unsuccessful HSCT - successful subsequent HSCT	0.67		Buckley 2011 - Unclear survival period. Note NZ rate - 1 case of 1 died.
Probability - late detection - unsuccessful HSCT - subsequent HSCT - PTS	0.40		Estimated from Railey (2009), Patel (2009)
Probability - late detection - unsuccessful HSCT - subsequent HSCT - no PTS	0.50		As above
Additional screening option probabilities			
Probability - early detection - test sensitivity	0.999		Baizen Ltd (2012) summary of US pilot data
Probability - early detection - test specificity	0.996		Baizen Ltd (2012) summary of US pilot data
Probability - number of positive tests that require a second TREC assay	0.920		Kwan et al 2013 (California) confirmatory testing algorithm
Probability - number of positive tests that require flow cytometry	0.180		Kwan et al 2013 (California) - Conservative estimate as not adjusted for true positives

Assumption	Value	Discounted - NPV	Comment
Costs			
Costs - early detection - HSCT	$70,194	-	Based on 2013/14 WIES price for Allogenic BMT, and estimated follow-up costs
Costs - late detection - excluding HSCT	$141,271	-	Based on cost analysis of 8 SCID cases - from national datasets
Costs - late detection - including HSCT	$254,938	-	Based on cost analysis of 8 SCID cases - from national datasets
Costs – late detection – additional HSCT	$157,435	-	Based on cost analysis of 8 SCID cases - from national datasets
Costs – post-HSCT support – specialist follow-ups – N PTS	$6,854	$6,615	Specialist follow-ups for five years following HSCT (17 visits in total at 13/14 prices discounted over time)
Costs - post-HSCT support - early detection	$39,838	$1,032,664	Based on figures provided by ADHB for IVIG per year (Adults) and 13/14 specialist follow-up price (12 visits per year)
Costs - post-HSCT support - late detection	$39,838	$830,986	Based on figures provided by ADHB for IVIG per year (Adults) and 13/14 specialist follow-up price (12 visits per year)
Costs - initial screening costs per screen	$5.22	-	Based on figures provided by LabPlus
Costs - confirmatory screening costs per screen	$369	-	Based on figures provided by LabPlus
Costs – first HSCT donor procurement	$45,000		Based on ADHB figures - range $10k to $80k. Assume no matching costs for subsequent. HSCTs
Costs – early detection – post-HSCT cost of dying – life-years 2 - 10	$38,584		Based on Chan & Jackson et al 2011. 2008 costs inflated to 2013/14 based on national prices (07/08 - 13/14)
Costs – late detection – post-HSCT cost of dying – life-years 2 - 10	$68,456		Based on Chan & Jackson et al 2011. 2008 costs inflated to 2013/14 based on national prices (07/08 - 13/14)
Outcomes			
Post treatment period - early detection – length of treatment	Lifetime	-	As noted in McGhee et al (2005) and Myers et al (2002)
Post treatment period - late detection – length of treatment	Lifetime	-	As above
Subsequent treatment - Number of additional HSCT	1		Clinical expert estimate. International literature cites some requiring multiple boosters
Survival years - early detection successful HSCT w/o post-treatment support	60.8	25.92	Based on Pai et al (2014) 5-yr survival & Statistics NZ life tables (2010-2012)
Survival years - early detection successful HSCT w post-treatment support	71.5	27.05	Assumption of 15% shorter life span
Survival years - late detection successful HSCT w/o post-treatment support	35.5	20.86	Based on Pai et al (2014) 5-yr survival, Buckley (2011) 10-year overall survival & Statistics NZ life tables (2010-2012)
Survival years - late detection successful HSCT w post-treatment support	41.8	22.55	Assumption of 15% shorter life span
Survival years - early detection - unsuccessful HSCT	1.44	1.43	Estimated from Chan et al (2011)
Survival years - late detection - unsuccessful HSCT	1.44	1.43	Based on Chan et al (2011), New Zealand data
Survival years - early detection - no HSCT	1.00		Assumption
Survival years - late detection - no HSCT	1.00		Based on Chan et al 2011

Transition probabilities

We have estimated a range of transition probabilities for cost-effectiveness modelling. Where possible we have linked these to evidence from the international literature and New Zealand SCID case histories. In other instances, we have been required to make estimates with clinical expert assistance. In many cases the probabilities of successful outcome of HSCT and need for post-transplant support relate to the quality of the match of donor and recipient. We have not attempted to model to that level of detail, but note that the probabilities used relate to the experience of the larger units reporting their results in the literature. Local experience is of a high level of matching and perhaps a lower use of post-transplant support treatments – estimates as used here are likely to be conservative.

In terms of the screening test, LabPlus advise that the only test they would consider is the TREC assay. This was described in the accompanying literature review, and would be a simple addition to the current newborn metabolic screening programme. Other tests have been assessed, but the TREC assay is the clear leader. Experience with the test in the US has been extensive, and has found extremely high sensitivity and specificity rates. There is no reason to expect there will be any difference in implementing the test here – other metabolic screening carried out in New Zealand equals or exceeds US figures. We have used the Californian protocol to estimate re-testing rates as it has been described in the most detail in the literature, but our understanding is that all the US programmes use reasonably similar protocols. This protocol uses a cut-off of 40µg/ml for re-testing on a second dried blood spot, with continued low results followed up with flow cytometry. LabPlus felt this was a reasonable approach (Dianne Webster, personal communication).

Costs

Base-case costs include treatment-related costs (eg, HSCT), donor procurement costs for first HSCT, specialist care post-HSCT, post-treatment support (mainly Intravenous immunoglobulin (IVIG)[2]), and TREC assay and confirmatory testing (includes full blood count and flow cytometry). In light of the survival curve for late detected cases of SCID (Figure 2 below), the costs associated with additional treatments in years two to ten of a child's life who has received an HSCT have been estimated.

Children who have their SCID detected late generally have a history of infections and other health conditions that require hospitalisation and specialist care. We have based the costs of late detected SCID on the case histories of the eight children who have been identified with SCID in the past 13 years in New Zealand. We have inflated costs to 2013/14 using national cost-weights and prices.

The primary treatment for SCID is HSCT (~80% of SCID cases). This is the case for both early and late detected SCID. We have based SCID treatment costs on HSCT, with HSCT costs for early detected cases based on the national 2013/14 WIES cost-weight for allogenic bone-marrow transplants. Specialist support post-transplant is assumed through immunology outpatient visits at national 2013/14 WIES cost-weights. We assume that children who are identified early through screening or family history only incur hospitalisation costs for HSCT. The usual post-transplant outpatient support regime at ADHB was costed at 2013/14 IDF price. For late detected SCID patients we have used the average inpatient cost of the New Zealand late detected cases identified for inpatient costs, and the anticipated outpatient support regime.

We have used the cost of intravenous immunoglobulin (IVIG) as the basis for post-treatment support costs of SCID patients who require such support. In some instances, SCID patients may also require antibiotic cover and immunosuppressant drugs post-HSCT, but we have not explicitly modelled these. Auckland DHB has provided an estimate of IVIG costs per year for adult patients who receive IVIG every 3-4 weeks following HSCT. We have used this estimate as the base-case cost for post-treatment support, although it is possible that IVIG costs will be more or less for children.

[2] If the transplant is not completely successful additional immunoglobulin support may be required. This usually takes the form of 4-weekly Intravenous immunoglobulin (IVIG).

LabPlus manages the testing for the newborn screening programme. They have advised that the list price for the TREC assay equates to approximately NZ$9.40 per test for 60,000 births. However, LabPlus expects this to be discounted for the size of the contract, and also as advised by suppliers keen to increase uptake of this screening test. To this reagent cost is added costs for one FTE laboratory technician to carry out the testing, and the usual laboratory overheads. This gives $5.20 per TREC assay as our base-case cost per test, with sensitivity analysis to show the range if varied.

LabPlus has also advised that the cost per flow cytometry as part of the confirmatory testing for positives is approximately $360 (excluding GST) and $9.83 for a full blood count. We have used these costs as the basis for confirmatory testing, primarily for false positives.

Health system costs for procuring donors are estimated to range from $10,000 to $80,000 based on the extent of the matching required, and where the marrow needs to be obtained from (eg, from US would be at the higher end of the range).[3] In the absence of any volume data we have used the mid-point of this range as an estimate of donor costs.

The potential costs associated with a child dying between ages two and ten has been estimated from a Jackson & Chan et al (2011) study of the costs associated with dying in Counties Manukau DHB in 2008. This is used as a proxy cost for the public system treatments needed additional to IVIG in the post treatment phase due to SCID.

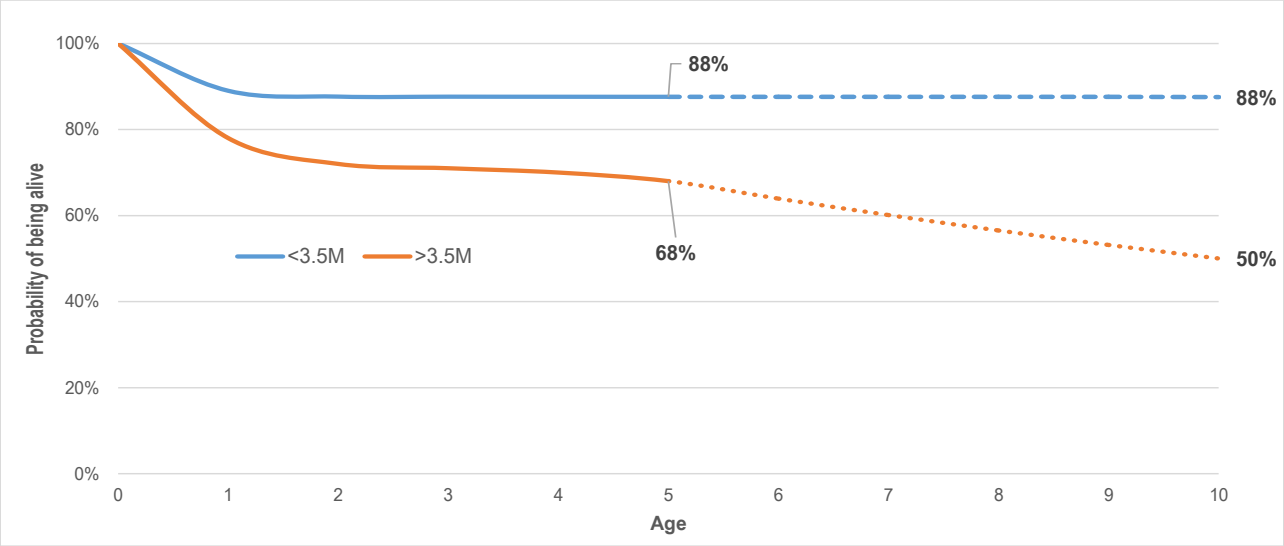
Outcomes

The duration of post-treatment support is somewhat of an unknown, as cases have yet to survive for long periods. We have assumed conservatively that this would be a lifetime cost for those who need it.

There is a significant amount of uncertainty regarding the long-term outcomes of SCID patients who receive HSCT. We have used published large case series findings of 5-year and 10-year survival of SCID patients (Buckley 2011, Pai et al 2014) (Figure 1) who have received a HSCT, and Statistics New Zealand life tables for the period 2010-2012, to estimate whole-of-life survival for these patients (Figure 2). Using this approach, we estimate that a SCID patient who has an HSCT prior to 3.5 months of age might expect to live on average 72 years, while a patient who has an HSCT after 3.5 months might expect to live on average 42 years. This compares to an estimated New Zealand population life expectancy of around 81 years.

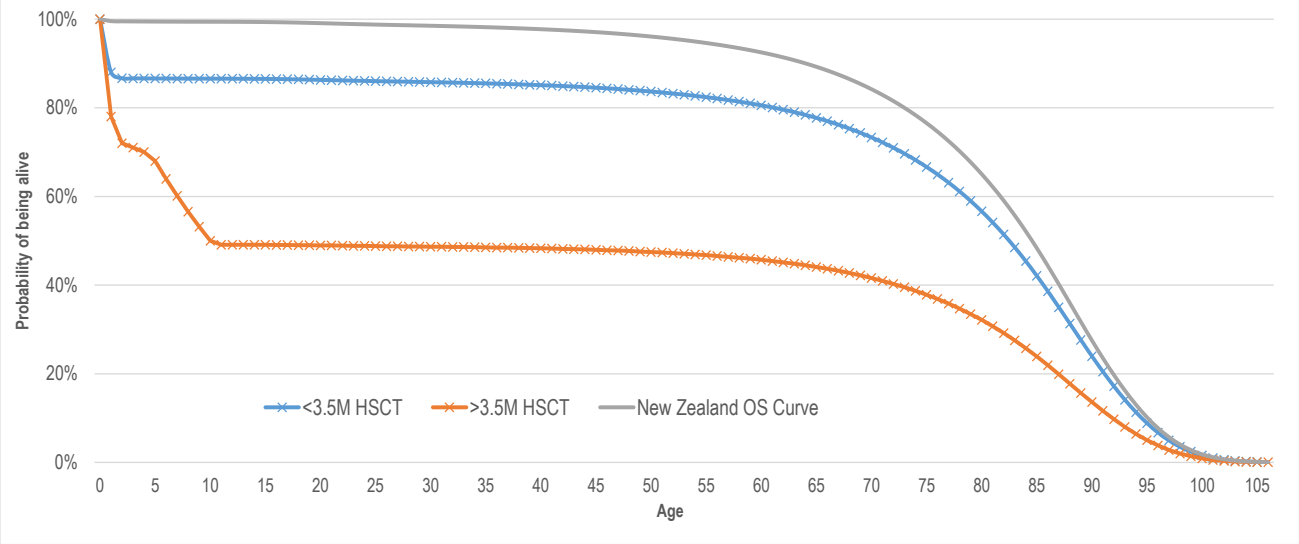
[3] New Zealand Blood Service, personal communication.

Figure 1 : Estimate of 5-year and 10-year survival outcomes of SCID patients who receive HSCT by age at treatment



Source: Constructed from Buckley 2011, Pai et al 2014

Figure 2 : Estimated whole-of-life survival curves for SCID patients who receive HSCT by age at treatment



Source: Health Partners constructed model

The New Zealand average survival outcomes of patients who did not receive a transplant (11 months) was used as the value for non-transplant cases. Only one case had an HSCT and subsequently died (at 10 months), so we looked to the literature for a more representative value. Chan et al (2011) have reported survival outcomes for children with SCID who were detected late and either did not receive an HSCT or who had an HSCT and subsequently died (see Table 5). We have used this estimate as the basis for survival outcomes of children who identified both late and early where HSCTs are ultimately unsuccessful.

Table 5 : Age of clinical events in SCID patients from survey of physicians and families of SCID children (n = 39) (months [mean +/- standard deviation]). Chan et al (2011)

	Diagnosis	Treatment	Death
SCID infants identified early+ (n=7)	1.0 +/- 0	3.7 +/- 4.3	All alive
SCID infants identified late- (n=32)	9.0 +/- 7.6	9.6 +/- 5.4	17.6 +/- 10.4%
SCID infants w HSCT (n=23)	6.9 +/- 5.0	9.8 +/- 5.5	17.3 +/- 7.5**
SCID infants w no HSCT$ (n=8)	15.4 +/- 10.3		19.4 +/- 14.0
SCID infants w PEGADA^ (n=1)	7	7	8

+ identified early is based on known family history of SCID, prior to manifestation of infections
- identified late is defined as confirmed with SCID after manifestation of infections
% 20 out of 32 SCID identified late died
** 10 out of 23 SCID patients transplanted died
$ all 8 SCID patients without HCT died
^ PEG-ADA specifically for SCID with adenosine deaminase deficiency

Discount rates

We have used a discount rate of 3.5% for both costs and outcomes. This is the rate used by PHARMAC and other government agencies, allowing direct comparison with other analyses. As outcomes here are believed to deliver full lifetimes, the discount rate truncates the 'net present value' of life-years gained – a 72-year gain reduces to 27 years when discounted. The effect of varying of the discount rate is shown in sensitivity analyses.

Findings

Base-case

Base-case assumptions suggest that on average the public health system currently spends approximately $157k per year on SCID for a gain of 4.1 life-years (see Table 6)Table 6 : . That is, no screening, and relying on opportunistic clinical diagnosis. Based on the same set of assumptions, adding newborn screening for SCID to the NMSP may result in saving 10.0 life years at a cost of $30k per life-year.

We estimate that the total cost of adding newborn screening for SCID to the NMSP inclusive of treatment costs would be around $460k per year. The net cost impact to the public health system would be around $303k per year.

Table 6 : Base-case estimate of the cost-effectiveness of adding newborn screening for SCID to the NMSP

Results	Costs	Life-years	Cost/LY
No screening	$157,092	4.1	
Screening	$460,166	14.0	
Net impact	$303,073	10.0	$30,409
ICER (cost per life-year gained)			$30,409

Our base-case assumption based on New Zealand experience is that an infant with SCID who does not receive an HSCT has an average life expectancy of ~1 year. We assume that life expectancy of children with SCID who do receive an HSCT is influenced by whether their condition has been diagnosed and treated early or late, and whether they require post-treatment support (mainly (IVIG). Based on these assumptions we estimate the following per SCID case (undiscounted) life-year scenarios:

1. No screening, no treatment – life expectancy 1 year, life years gained 0;
2. No screening, late treatment – life expectancy 36-42 years, life years gained 35-41 years;
3. Screening, early treatment – life expectancy 61-72 years, life years gained 60-71 years.

Table 7 provides a breakdown of screening scenario cost components. We estimate costs of initial screening (TREC assay) at $310k (59,431 children * $5.22 per test) and the costs of false positives at $16k. False positive costs include a second TREC assay and flow cytometry for infants who require these.

Table 7 : Screening scenario cost components – base-case assumptions

Screening option cost components	$	% costs
Initial screening	$310,229	67%
Confirmatory testing & treatment - SCID cases	$134,216	29%
False positives - confirmatory testing	$15,721	3%
Total	$460,166	100%

No screening option costs	$157,092
Net cost impact	$303,073

We estimate a break-even (ie, no net cost impact from adding newborn screening for SCID to the NMSP) cost per TREC assay as $0.14, a reduction of $5.08 from the assumed cost of $5.22 per assay[4]. This analysis includes the assumed number of secondary TREC assays resulting from false positive screens (estimated at 219).

Table 8 : Break-even analysis of cost per TREC assay

Assumed cost per TREC Assay	$5.22
Number of TREC Assays (incl confirmatory)	59,650
Total TREC Assays costs less net impact	$8,300
B/E cost per initial screen	**$0.14**

A screening programme for SCID may considerably reduce the cost of death of diagnosed children aged two to ten years who have had an HSCT (Table 9). This is due to there being considerably more deaths of late detected SCID cases in the first 10 years of life, resulting in higher cost to the public health system relative to early detected SCID cases.

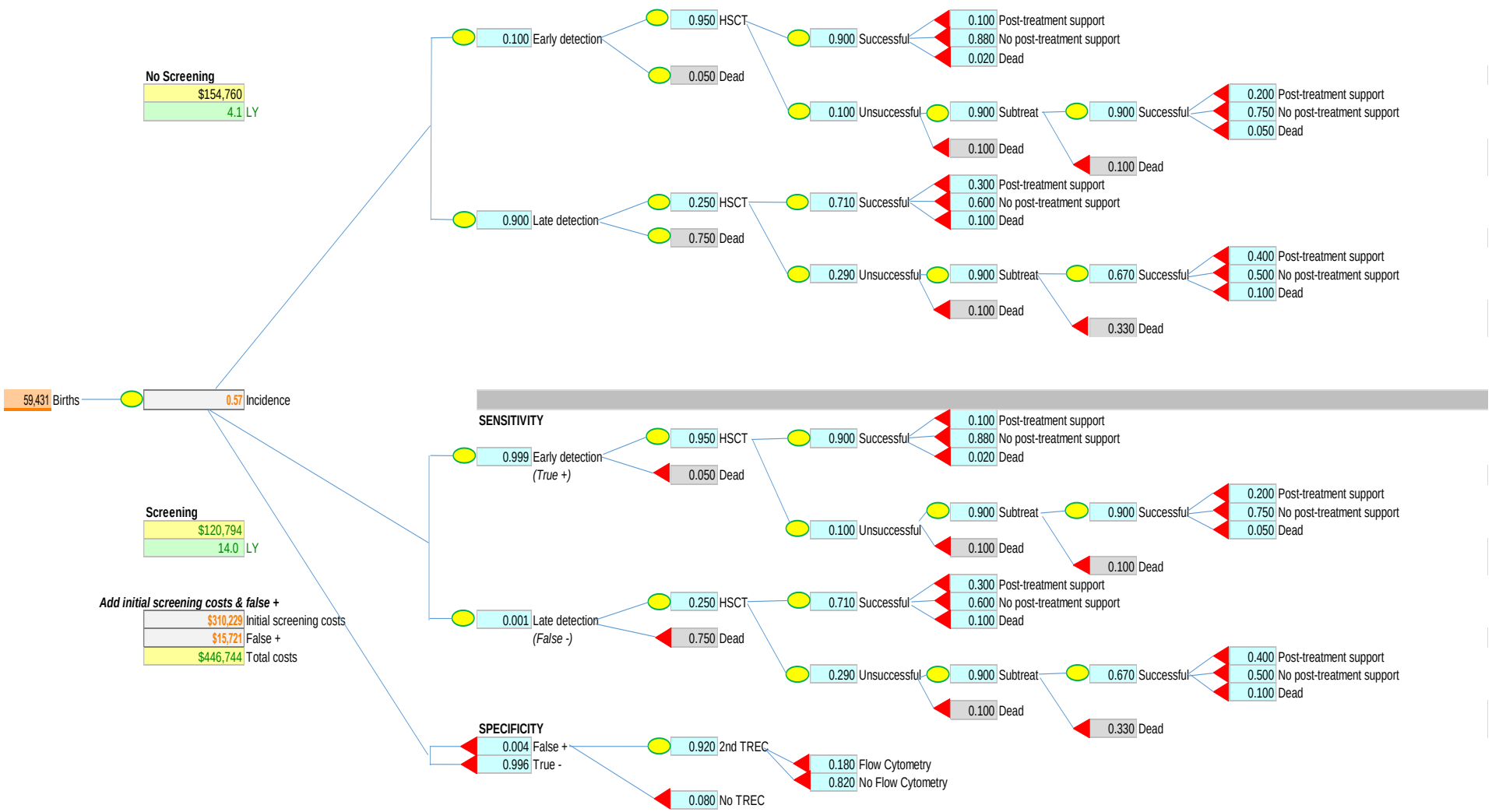
Table 9 : Estimated cost of deceased cases following HSCT between two and ten years of age (costs discounted)

Measure	Total Cases	Cases deceased	Cost of deceased cases
NS - early	0.06	0.01	$255
NS - late	0.51	0.26	$15,227
S - early	0.57	0.07	$2,550
S - late	0.00	0.00	$182

Note: No screening (NS); screening (S)

[4] Note this would represent a reduction of $9.26 from the test reference cost advised by LabPlus.

Figure 3 : Base-case decision tree showing transition probabilities, costs and life-years for no screening and screening options (also in Appendix 2 at A3 size)



Sensitivity analysis

We have conducted univariate sensitivity analysis of key model parameters: incidence rate, survival outcomes, and treatment costs associated with early and late detection.

Incidence rate

New Zealand's past 13-year SCID incidence rate is relatively low when compared to incidence rates cited in the international literature, suggesting it is likely that some cases of SCID in New Zealand have not been identified over this period. If this is the case, the incidence rate in New Zealand will be higher than we have assumed in the screening option.

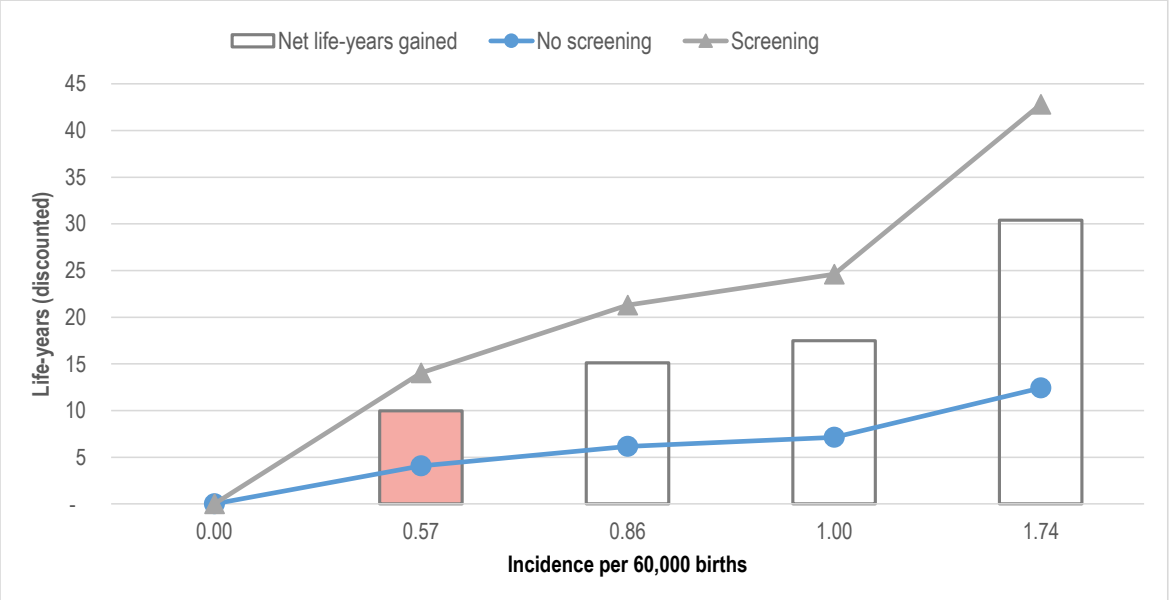
The assumed rate of SCID has a pronounced effect on the potential cost-effectiveness of adding newborn screening for SCID to the NMSP, as shown in Table 10. If a screening programme in New Zealand revealed the SCID incidence rate to be closer to the average rate US observed rate, this would result in a lower cost per life-year gained from screening. Indeed, this would reduce the incremental cost per life-year gained from $30k to $19k, a reduction of $11k.

Table 10 : Economic impact of different SCID incidence rates based on the observed 13-year New Zealand rate and international evidence

	NZ rate (13-yr trend)	Average US pilot rate	Lowest US pilot rate	Highest US pilot rate	Assumption of 1 case per year
Incidence	104,215	68,709	-	34,159	59,431
Incidence per 60,000 births	0.57	0.86	0.00	1.74	1.00
Total Costs					
No screening	$157,092	$238,272	$0	$479,273	$275,470
Screening	$460,166	$529,543	$325,912	$735,506	$561,333
Net costs	**$303,073**	**$291,271**	**$325,912**	**$256,233**	**$285,863**
Life-years					
No screening	4.1	6.2	-	12.4	7.1
Screening	14.0	21.3	-	42.8	24.6
Net Life-years	**10.0**	**15.1**	**-**	**30.4**	**17.5**
COST/LY					
No screening	$31,471	$38,599	$0	$38,599	$38,599
Screening	$27,396	$24,873	$0	$17,175	$22,806
ICER	**$30,409**	**$19,268**	**NA**	**$8,427**	**$16,357**

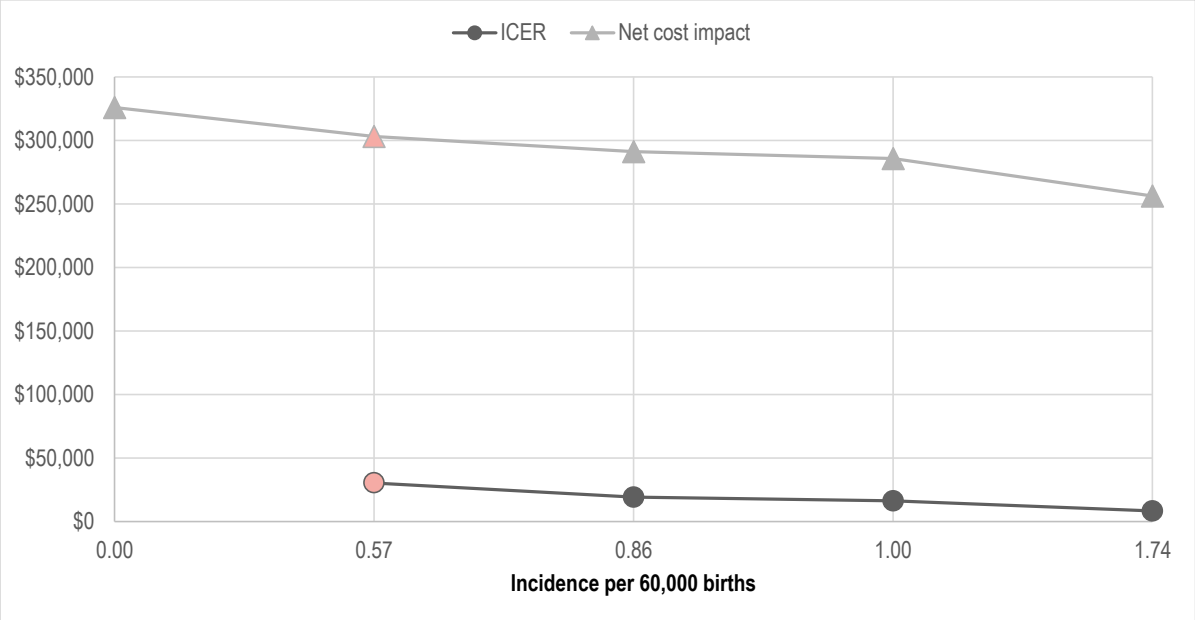
Figure 4 shows that as the incidence rate increases, more life-years are gained irrespective of whether a screening programme is in place. However, as noted above, screening may reveal a higher number of cases than previously identified under the current regime of opportunistic diagnosis. This would suggest that life-years gained may be greater than depicted if a screening programme were in place.

Figure 4 : Relationship between life-years gained and incidence rate for no screening and screening options



As shown in Figure 5, there is a net cost impact for the public health system regardless of the SCID incidence rate. The assumed efficacy of identifying SCID early through a screening programme offsets some of the net cost impact since life-years gained are greater with screening than without.

Figure 5 : Relationship between ICER and new cost impact of screening relative to no screening for different SCID incidence rates



Survival - life expectancy

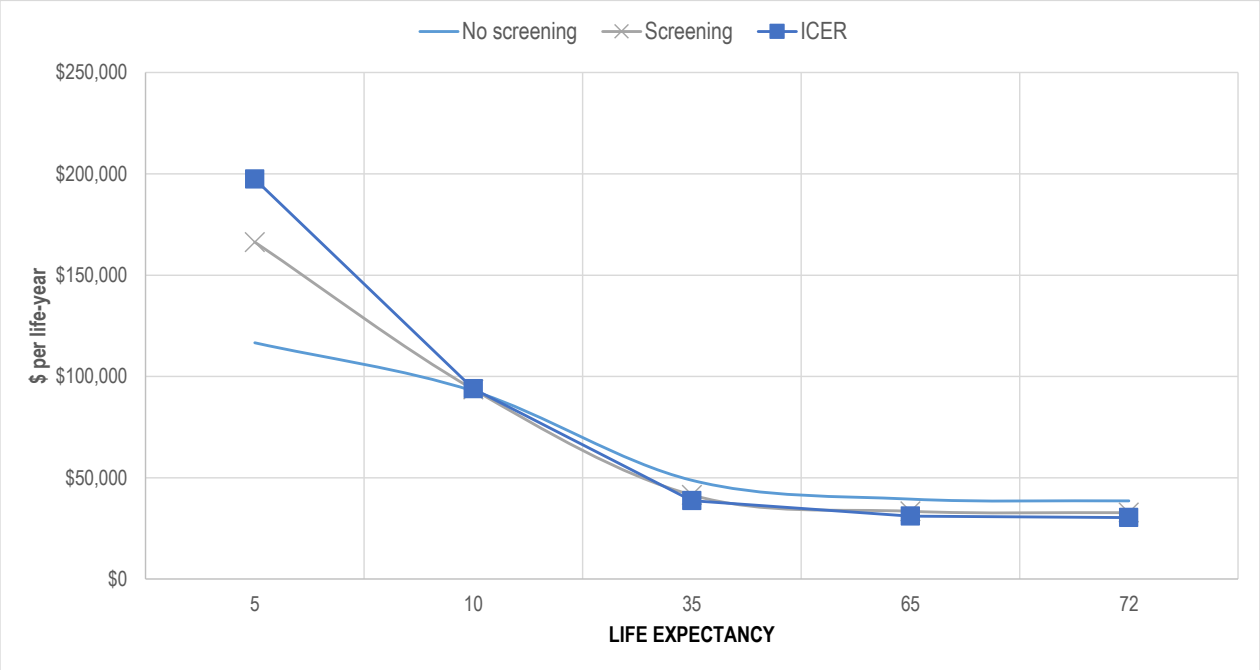
There is significant uncertainty regarding the life expectancy of children with SCID who receive HSCT. To account for some of this uncertainty, we have conducted sensitivity analysis using a range of survival periods ranging from 5 years to an estimated average life expectancy (see Methodology section for further detail). As shown in Table 11 and Figure 6, at shorter periods of survival (5 to 10 years of life), the cost per-life year gained is greater for the screening option than the current regime of opportunistic diagnosis. However, at longer periods of survival, 35 years and over, cost per life-year is less for screening than opportunistic diagnosis.

Table 11 : Economic impact of different life expectancy scenarios – base-case incidence assumption (New Zealand 13-year observed rate)

Life expectancy scenarios	5-yr survival	10-year survival	35-year survival	65-year survival	Estimated life expectancy
Undiscounted value - early detection	5.0	10.0	35.0	65.0	71.5
Discounted value - late detection	4.7	8.6	20.7	26.4	27.0
Undiscounted value - late detection	2.9	5.9	20.6	38.2	41.8
Discounted value - late detection	2.8	5.4	15.0	21.6	22.5
Total Costs					
No screening	$109,934	$129,448	$144,642	$155,506	$157,092
Screening	$407,254	$417,945	$444,176	$458,400	$460,166
Net costs	**$297,320**	**$288,498**	**$299,534**	**$302,894**	**$303,073**
Life-years					
No screening	0.9	1.4	3.0	3.9	4.1
Screening	2.4	4.5	10.7	13.7	14.0
Net Life-years	**1.5**	**3.1**	**7.7**	**9.8**	**10.0**
COST/LY					
No screening	$116,635	$92,817	$48,769	$39,478	$38,599
Screening	$166,313	$93,613	$41,493	$33,465	$32,784
ICER	**$197,401**	**$93,975**	**$38,704**	**$31,038**	**$30,409**

Assumptions: Patients who receive post-treatment support live 15% shorter lives than those who do not, irrespective of total length of life. The relative difference in life expectancy between early and late detected SCID patients remains the same irrespective of total length of life. Note 5-year survival excludes cost of dying estimate.

Figure 6 : Impact on cost per life-year of different life expectancy scenarios – base-case incidence assumption (New Zealand 13-year observed rate)



Treatment costs

Sensitivity analysis of treatment costs suggests marginal impacts on the incremental cost per life-year gained from screening (see Table 12) (+/- $1,600).

Table 12 : Impact of treatment cost scenarios on incremental cost per life-year gained – base-case assumptions

Cost scenarios	Base-case	Plus Standard Error	Less Standard Error
No screening	$157,092	$178,777	$135,408
Screening	$460,166	$466,088	$454,243
Net costs	**$303,073**	**$287,311**	**$318,836**
ICER	**$30,409**	**$28,828**	**$31,991**

Discount rate

Since the modelled benefits of early detection of SCID largely relate to the length of life of patients, much of the benefit occurs in the future (ie, later life-years). If a discount rate is applied, these future benefits appear smaller given the assumption that benefits that occur in the future are less valuable relative to benefits that occur closer to the present. In contrast, most of the costs associated with SCID are assumed to occur within the first year of a child's life; these costs are not affected by the application of an annual discount rate.

Table 13 provides an assessment of the impact of different discount rate scenarios. It shows that the incremental cost per life-year is sensitive to the discount rate applied. For example, if funder (and patient) indifference is assumed between present and future benefits and costs (0% discount rate), the incremental cost per life-year reduces by $20k (or 66%).

Table 13 : Impact of discount rates on costs, life-years and incremental cost per life-year gained

Discount rate scenarios	Base-case (3.5%)	0%	5% 0% Outcomes; 3.5% Costs	
No screening	$157,092	$188,666	$149,701	$159,433
Screening	$460,166	$540,315	$446,330	$460,204
Net costs	**$303,073**	**$351,649**	**$296,629**	**$300,772**
No screening	4.1	8.1	3.3	8.1
Screening	14.0	36.6	10.6	36.6
Net Life-years	**10.0**	**28.5**	**7.3**	**28.5**
ICER	**$30,409**	**$12,358**	**$40,692**	**$10,570**

Willingness-to-pay thresholds per life-year gained

Public health system funding and prioritisation decisions are not formally based on pre-determined willingness to pay thresholds per life years gained. However, for indicative purposes we have assessed the SCID incidence rate and TREC assay cost per test respectively that would be required to meet indicative willingness to pay thresholds (see Table 14).

We note that the SCID incidence rate is not within the scope of public health system influence. Nonetheless, given the uncertainty regarding the New Zealand SCID rate we believe that, alongside the earlier incidence rate sensitivity analysis, estimating the incidence rate required for cost per life-year thresholds is informative for decision makers. To meet a $15,000 per life year threshold one would need the incidence to be less than the US pilot average (1 for every 55,100 births); or if the incidence remained at 1 in 104,000 births the cost of the test would need to drop to $2.64 (all other parameters remaining the same).

Table 14 : Willingness-to-pay thresh-holds per life-year gained based on alternative incidence scenarios and cost per screening test

Willingness-to-pay thresholds	$5,000 per LY	$15,000 per LY	$30,000 per LY	$50,000 per LY
Incidence (other parameters base-case)	1:23,250	1:55,100	1:102,900	1:166,650
TREC Assay cost (base-case incidence)	$0.97	$2.64	$5.15	$8.49

Discussion

We have constructed a decision tree-based cost-effectiveness analysis of adding SCID screening to the existing newborn screening programme in New Zealand. The recent introduction and evaluation of SCID screening in the US, and the publication of several case series of the outcomes of HSCT in SCID screening have allowed some reasonably firm estimates to be used to construct the model. We have deliberately constructed the base-case to be conservative; in the base-case, the introduction of SCID screening would appear to cost less per life-year than the current regime of opportunistic diagnosis. The programme would cost $310k per year in 2013/14 dollars for the health system to implement, with an additional cost of $150k for confirmatory testing and treating cases of SCID (total cost $460k). However, the net cost to the public system would be $303k, which we estimate would save an additional 10 life-years (discounted) at an incremental cost of $30k per life-year.

With the constructed model, all variables can be tested in appropriate ranges. The most sensitive were the underlying incidence rate, and the cost of the test. The base case uses an incidence of one SCID case per 104,215 births, based on eight identified cases in 13 years in New Zealand. The expert panel believes that the actual rate is likely to be higher than this, more in line with the US and Australian figures of around 1 per 60,000 births. If this holds then the incremental cost per life-year gained would fall to $16k.

If the cost of the test was $9.40 (approximate reference cost inclusive of DHB overhead charge), then the cost per life year would increase to $55k. An incidence of 1 per 58,300 births would be needed to bring the cost per life years back to $30k per life year. If the cost of the testing was a barrier one could consider screening only boys, as they are noted as being at higher risk of SCID in the literature. However we would note the existing data for New Zealand has a 50/50 split between males and females.

The costs of HSCT are incurred irrespective of diagnostic regime – that is, in screening and in no screening scenarios. There is clear evidence in the international literature of significantly increased cost for late-detected SCID compared to early-detected. Some of this cost difference can be explained by late detected SCID HSCT patients requiring longer hospitalisation and care immediately following the HSCT procedure (Chan et al, 2011). The average cost of the three HSCTs undertaken in New Zealand for infants with SCID is 2.2 times greater than the national average WIES cost for HSCT. Our base-case assumes that on average, the costs of early detection SCID HSCT will be at the national average WIES cost. If, on the other hand, the average cost of early detected SCID cases were at the average cost of New Zealand's experience of late detected SCID, the net cost to the public system would be $401k and the incremental cost per life-year gained would increase to $40k – an increase of $10k. This represents a material increase on our base-case estimate. We consider this scenario unlikely in light of international evidence regarding cost differences between late and early detected SCID. Indeed it may be more likely that we are underestimating the differential between early and late HSCT – up to four-fold differences have been detailed in the US context.

Less certain are the survival/life expectancy ranges expected after the various iterations of HSCT, 2 HSCTs, with post-treatment support/without etc. We have constructed from the case series published in the literature, and, with expert clinical help, a plausible series of survival curves, and probabilities for each iteration. However, the actual outcomes in the New Zealand context may vary from these. As each branch of the model has a relatively low probability of occurring, varying the survival chances through plausible ranges made little difference to the final cost per life year figures, which is reassuring.

In addition to finding classical SCID cases, the screening programme will identify other immunodeficiency and variant syndromes. For example, the Californian programme found one 'variant' SCID for each case of classical SCID, and a further 0.6 cases with other syndromes. The early detection of these cases might be expected to be a net gain for the health system in terms of reduced investigatory testing, but little evidence exists as to the benefits or otherwise of early treatment. Additional treatment costs might be engendered, for some unknown health gain. Each individual syndrome is rare, and difficult to model. If the screening

programme can be justified by finding classical SCID, as examined here, then attempting to quantify the non-SCID cases is unlikely to be beneficial at this stage.

For most cost effectiveness analyses of screening programmes, the sensitivity and specificity of the test feature strongly. In this case, the test is a very good one, with a very high sensitivity and specificity, and there is extensive experience with it, allowing very tight estimate of the likely range in the New Zealand setting. With the infrastructure of the newborn screening programme already in place there would be very little additional cost apart from the test costs as noted above. The cost of treatment of cases found is more than outweighed by the averted cost of inpatient care and the added cost for late HSCT if no screening takes place.

Conclusion

Based on the evidence of screening for SCID in the US, with the assumptions as developed above, the cost-effectiveness of adding screening for SCID to the New Zealand NMSP would appear to be in line with existing heath care interventions, at an estimated cost of $30k per life year.

Appendix 1 – SCID incidence in New Zealand

We constructed a data query for the national data collections to search for all children who have ever received a diagnosis of SCID in New Zealand over the past 13 years, 2000 to 2013, through either hospital coding or in the mortality data. All cases of childhood infection and immunodeficiency investigation would occur in the public health system in New Zealand, and be recorded in the national data collections. New Zealand's NHI health identifier allows records to be linked to ensure each case is only counted once.

The codes used were ICD-10 code D81x covering the diagnosis of 'SCID', and the main related diagnoses. This identified 13 individuals. These were then compared with clinical databases, which resulted in six of these cases being confirmed, and a further two cases known to clinicians but not identified initially being found, resulting in a total eight cases being confirmed. Two cases received bone marrow transplants (one twice), for one to survive. All others died. One case was only diagnosed on death. It is likely other cases of immunodeficiency were not identified in the time period, meaning the estimated number of cases is likely to be an estimate.

Once each case was determined, an anonymised query extracted all contact recorded for those individuals in the public health system. No identifiable data is held.

Summary

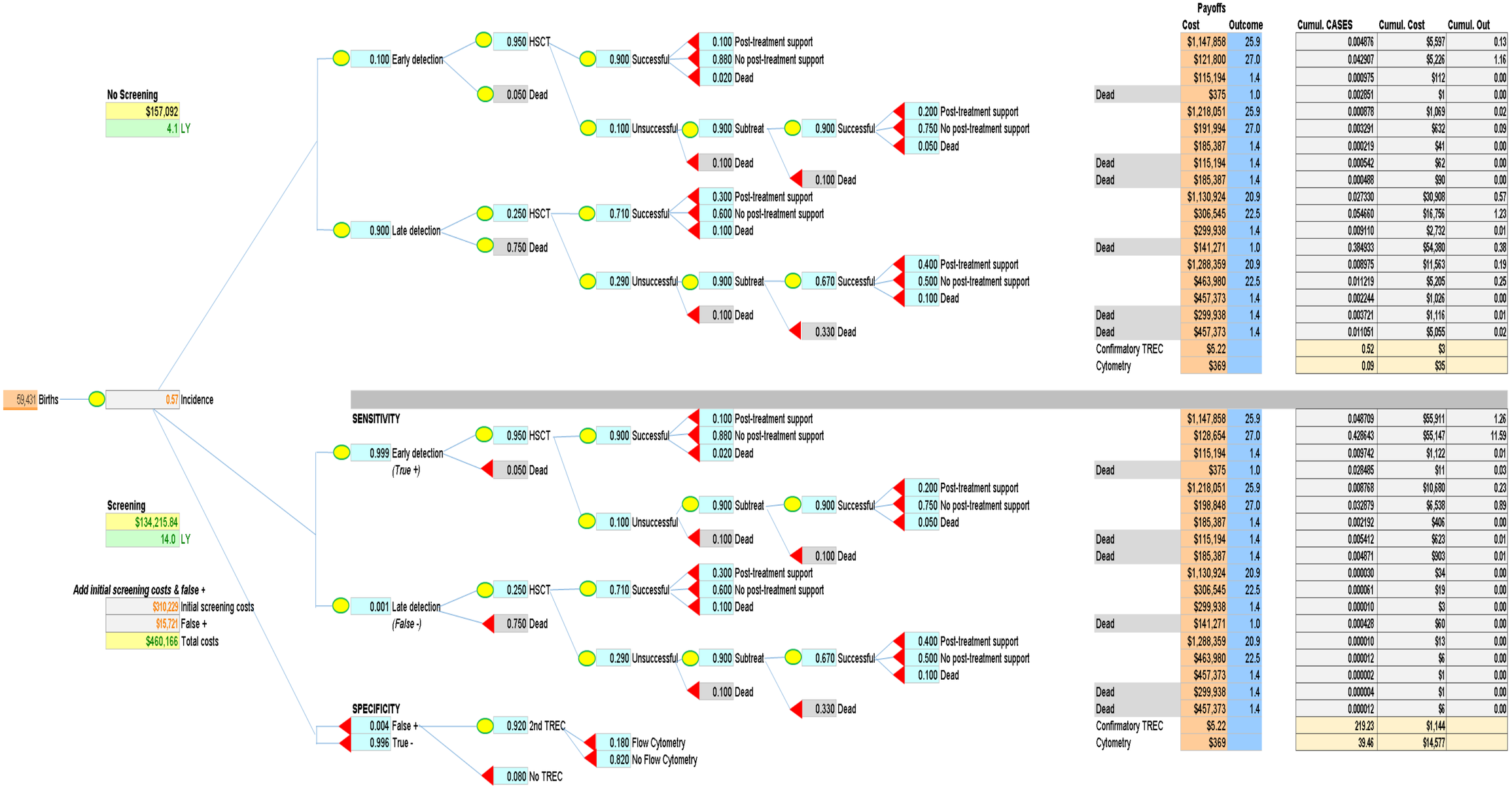
Cases:	8 - 4 male, 4 female
Years covered :	2000 – 2013; birth incidence 1:104,215 births
Deaths:	7 of 8. Average age at death - 11 months, range 2-22 months
Ethnicity:	3 Indian, 2 Pacific, 1 Māori, 1 European, 1 Other
HSCT:	2 cases, 1 at age 4 months following infections and liver failure, and 1 first at 10 months of age. Both thus 'late' transplants

Estimated costs are shown based on the prices DHBs would pay for these services through the Inter-District Flow (IDF) price schedule. While actual costs will vary from this for individual cases, the IDF prices match actual costs in aggregate. Costs exclude maternity and birth and any neonatal care costs.

Cost component	Derived from	Cost
Average cost total		**$218,930**
Average inpatient cost	WIES IDF price	$204,420
Average outpatient cost	IDF price	$7,830
Average ED cost	IDF price	$360
Average community pharmaceutical cost	IDF Price	$1,570
Average community laboratory testings cost	Cost	$30
Average travel & accommodation cost	Cost	$4,740

Travel and accommodation costs relate to those paid by DHBs to families only; any costs above this incurred by families are not included. Primary care costs were not available.

Appendix 2 – Base-case decision tree (A3)



	Payoffs Cost	Outcome	Cumul. CASES	Cumul. Cost	Cumul. Out
	$1,147,858	25.9	0.004876	$5,597	0.13
	$121,800	27.0	0.042907	$5,226	1.16
	$115,194	1.4	0.000975	$112	0.00
Dead	$375	1.0	0.002851	$1	0.00
	$1,218,051	25.9	0.000878	$1,069	0.02
	$191,994	27.0	0.003291	$632	0.09
	$185,387	1.4	0.000219	$41	0.00
Dead	$115,194	1.4	0.000542	$62	0.00
Dead	$185,387	1.4	0.000488	$90	0.00
	$1,130,924	20.9	0.027330	$30,908	0.57
	$306,545	22.5	0.054660	$16,756	1.23
	$299,938	1.4	0.009110	$2,732	0.01
Dead	$141,271	1.0	0.384933	$54,380	0.38
	$1,288,359	20.9	0.008975	$11,563	0.19
	$463,980	22.5	0.011219	$5,205	0.25
	$457,373	1.4	0.002244	$1,026	0.00
Dead	$299,938	1.4	0.003721	$1,116	0.01
Dead	$457,373	1.4	0.011051	$5,055	0.02
Confirmatory TREC	$5.22		0.52	$3	
Cytometry	$369		0.09	$35	
	$1,147,858	25.9	0.048709	$55,911	1.26
	$128,654	27.0	0.428643	$55,147	11.59
	$115,194	1.4	0.009742	$1,122	0.01
Dead	$375	1.0	0.028485	$11	0.03
	$1,218,051	25.9	0.008768	$10,680	0.23
	$198,848	27.0	0.032879	$6,538	0.89
	$185,387	1.4	0.002192	$406	0.00
Dead	$115,194	1.4	0.005412	$623	0.01
Dead	$185,387	1.4	0.004871	$903	0.01
	$1,130,924	20.9	0.000030	$34	0.00
	$306,545	22.5	0.000061	$19	0.00
	$299,938	1.4	0.000010	$3	0.00
Dead	$141,271	1.0	0.000428	$60	0.00
	$1,288,359	20.9	0.000010	$13	0.00
	$463,980	22.5	0.000012	$6	0.00
	$457,373	1.4	0.000002	$1	0.00
Dead	$299,938	1.4	0.000004	$1	0.00
Dead	$457,373	1.4	0.000012	$6	0.00
Confirmatory TREC	$5.22		219.23	$1,144	
Cytometry	$369		39.46	$14,577	