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RESEARCH ARTICLE

SEVERE COMBINED IMMUNODEFICIENCY SCREENING AND STEM CELL TRANSPLANT – AN ECONOMIC EVALUATION SCHEME

Husain Ahmed Alzobaidi¹, Abdul Rhman Alghamdi², Mohammad Eid Mahfouz³ and Rawan Dakhil Allah Alsubhi⁴

1. Consultant of Family Medicine & Public Health, Ministry of Health, Jeddah, Saudi Arabia.
2. Associate Professor of Family Medicine, Taif University, Taif, Saudi Arabia.
3. Laparoscopic and Thoracic Surgeon, Taif University, Taif, Saudi Arabia.
4. General Practitioner, King Abdullah Medical Complex, Ministry of Health, Jeddah, Saudi Arabia.

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Abstract

Background: Severe Combined Immunodeficiency (SCID) is a rare genetic disease that affects newborn immune system and costs healthcare system a substantial amount of money. Screening and stem cell transplant may offer a cost-effective alternative to the current medical practice.

Objective: To determine the cost-effectiveness of screening newborn for SCID with subsequent stem cell transplant versus standard of care.

Materials and Methods: An economic evaluation was proposed, using Treeage software on a set of evidence-based probabilities and variables.

Outcomes: as shown on the tree, we count the death from SCID. It's given the payoff 1, while the survival is payoff 0. The outcome of interest is death averted by screening live birth and implementing subsequent stem cell transplant for those who tested +ve.

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Introduction:-

Severe Combined Immunodeficiency (SCID) is a rare genetic disease that affects newborn immune system because of disturbed function and maturation of B-cell and T-cell lymphocytes. That distortion leads to a defective antibody response and hence compromised immunity^{1,2}. After birth, antibodies that passed from the mother protect the infant. That may last for several months, and then the affected baby starts to easily get multiple infections and eventually dies at age that varies from one to two years. Its overall incidence is estimated to be 1 per 66,000 live births³.

DNA TREC is a newly developed screening test that has been recently approved by FDA with sensitivity of almost 100%⁴. Data showed that the infants who received the bone marrow stem cell transplant at the age of 3.5 months or younger had a 5-yr survival rate of 94%⁴.

Objectives:-

To determine the cost-effectiveness of screening newborn for SCID with subsequent stem cell transplant versus standard of care.

Corresponding Author:- Husain Ahmed Alzobaidi

Address:- Consultant of Family Medicine & Public Health, Ministry of Health, Jeddah, Saudi Arabia, Former Fellow at Rollins School of Public Health, Emory University, Atlanta, USA.

Methods:-**(StudyDesign)⁵****Audience:**

This study may be used by Center for Medicare and Medicaid Services (CMS) or similar agencies around the world. It can be used for both program and policy decision-making as CMS is funding the purchase of medical services for current and alternate strategies for many affected infants across the states. Other parties might be interested in the result as the state governments, Managed Care Organization and insurance companies as for the they pay part or all the medical cost.

Study Question:

What is the cost-effectiveness of screening newborn for SCID with subsequent stem cell transplant versus standard care?

Standard care means the current medical practice of treating recurrent infections and maintaining a sterile environment as possible for those children with SCID.

Intervention Strategy:

using the TREC real time PCR kits⁶ to screen all born babies through blood sample which is highly sensitive (approaches 100%)⁴, followed by bone marrow stem cell transplant which is found to have 94% five-year survival rate.³

The target population are all the live births in the USA, and the test is performed before discharge of the baby, delivered by a pediatric nurse and interpreted by an immunologist or trained lab specialist. Infants who tested positive are candidates for bone marrow stem cell transplant within age of 3.5 months. The stem cell transplant will be carried out in specialized centers with experienced staff and the affected infants may need to be transported to those centers.

Perspective:

As the audience of this economic analysis is mainly CMS, the analysis looks at the federal level and to some extent to the state level as they fund purchasing the medical service for the target population. Societal cost, although important, is not considered in this analysis because this disease is very rare, and that will not affect the public health that much.

Time Horizons:

The time frame of this analysis is from 1 month to 1 year. During this timeframe, the stem cell transplant should be carried out and a steady state of health achieved. On the other hand, the analytic horizon would be 5-10 years as the survival follow-up may extend to that time. In fact, that horizon may extend for more years to lifelong, with average of 70 years, as the effect of stem cell transplant may last for lifetime. However, we assumed that CMS might not be interested in considering that long period in cost and effect analysis.

Analytic Method:

Decision tree was constructed using Treeage software (attached). The cost and effect were assigned to each decision terminal and cost-Effectiveness Analysis (CEA) will be conducted with costs expressed in current US dollar and the outcome is the death prevented by each strategy. An incremental analysis (ICER) will be used since the two strategies are different. The incremental analysis is intended to examine the relation between the investment in stem cell transplant and the survival expected to be produced by this intervention.

The probabilities assigned to each branch are as following:

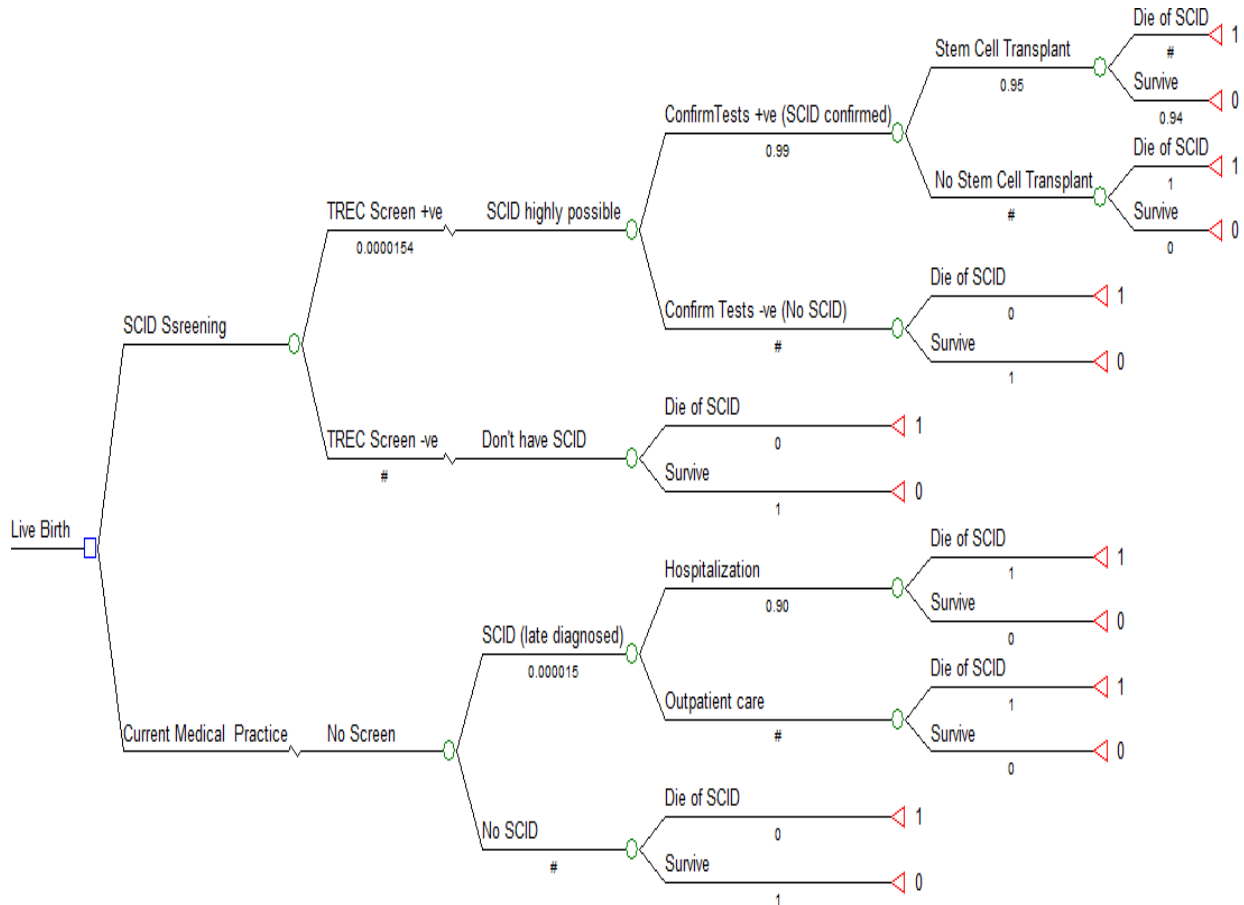
1- TREC screening test probability: 0.0000154. The incidence of SCID is 1 in 66,000 livebirth³, which is equal to 0.0000152. The TREC test is highly sensitive which means it excludes every non-SCID case (SnNout), however, it may include some false +ve cases. To accommodate for this, we assumed the the TREC's Positive Predictive Value (PPV) is 99% and thus the test would include 1% false +ve. We multiplied 0.01 by the incidence and added the result to the incidence. The expected TREC+ve test from all live births in USA is 0.0000154, which is a bit higher than the incidence.

2- The probability of confirmed SCID disease from those TREC screened +ve: 0.99. This actually resembles the TREC sensitivity. Sensitivity of 99% , instead of 100%, is used to be certain.

- 3- The probability of having stem cell transplant: 0.95. We assigned 5% of those confirmed SCID cases to NO stem cell transplant branch based on assumption of possibility of unavailability of HLA match cases for transplant, delay, or inability to perform it because of logistic reasons.
- 4- The probability of survival after stem cell transplant: 0.94^3 .
- 5- The probability of SCID diagnosis by current standards of care: 0.000015. It's assumed to be less than the incidence. It highly depends on the inclusion criteria and high index of suspicion by the treating physician. Most of the case are eventually diagnosed, but in a late terminal stage.
- 6- The probability of hospitalization of SCID diagnosed by current standards of care: 0.90. We assumed that outpatient including ER will provide some care, but no clear figure is available.
- 7- The probability of death from SCID without stem cell transplant: 1.
- 2- *The Costs:* The cost will be measured by Macro-coasting approach (gross costing) from top down⁷. The cost is expressed in the current dollar value (2019) and the average costs of the following variables will be counted for: the TREC screening test cost, the confirmatory testing, the bone marrow stem cell transplant, the inpatient hospitalization and outpatient visits. The TREC screening cost includes the reagent, analyzing machine, reader costs. The confirmatory testing costs include the test cost and hospital stay cost for the duration of testing if needed an admission. The stem cell transplant cost includes all necessary test cost for donors, matching test like HLA, anesthesia, procedure, labor and hospital stay costs. Inpatient hospitalization cost for those SCID patient not screened is expected to be highly variable because the severity of infections, type of treatment and hospitalization room (ICU vs. regular). For this reasons, an average estimate will be used per day of hospital stay. Outpatient visits cost includes physician consultation cost, medication cost, any test cost and ER visits if not admitted. The cost of TREC screening test is estimated to be \$ 5-7 depending on the state⁸. The cost of confirmatory testing is estimated to be \$ 250, which includes differential blood cell count and lymphocyte phenotyping⁹. The cost of stem cell transplant that would be delivered within 3.5 months from birth is estimated from literature to be \$ 120,000⁸. The cost of hospitalization will be estimated by calculating the average charges of inpatient with immune disease in the same age stage from Health Cost and Utilization Project (HCUP) Kid's database for the last year. The cost of an outpatient visit will be estimated by Medicare charges or multiplying the resources-based relative value scales units (RBRVUs) for the price of an office visit by Medicare conversion factor⁷.

Implicit costs such as travel cost, parent stay cost, and intangible cost like suffering are not considered in this direct cost analysis.

- 3- *The Outcomes:* as shown on the tree, we count the death from SCID. It's given the payoff 1, while the survival is payoff 0. The outcome of interest is death averted by screening live birth and implementing subsequent stem cell transplant for those who tested +ve. The cost and outcomes will be calculated by cost effectiveness ratio (ICUR).
- 4- *Uncertainty:* this analysis contains some uncertainty for it's based on many assumptions; some of them have been discussed above in probabilities. In addition to those assumptions, we assumed that all those who are not diagnosed by current medical practice are not considered SCID cases. In real practice, there are cases, which left undiagnosed until death either because of lack of proper diagnostic tools or because of large spectrum of immune diseases, but that does not mean they are not having SCID. This assumption will decrease the cost of current practice arm and may give better outcome result to that arm. We also assumed that only early stem cell transplant would be effective, however, late transplant has some successful results, yet more costly. This assumption will decrease the cost of screening arm and may give a more favorable result for the screening. We as well assumed that SCID is only one type, while in fact it is of several types with different tests and different successful treatment modalities like gene therapy for example. This assumption may include other different SCID types that irresponsive to stem cell transplant and gives less survival figures. Generally, those assumptions may affect the internal validity and reliability of this analysis. However, because SCID is very rare, such small figure changes based on previously mentioned assumptions may not have that large effect on the results and external validity (generalizability).
- 5- *Summary Measures:* as mentioned earlier, the incremental cost-effectiveness ratio will be reported to summarize the study results.
- 6- *Distributional effect:* as the screening test and subsequent stem cell transplant for infants with SCID are expected to be costly on the short run, there would be an expected shift for the cost money from some medical disease to SCID. However, if it is proved less costly and more effective than current medical practice on the long run, then the extra cost of current medical practice can be utilized to benefit other needy areas. CMS, states and Insurance companies will pay the cost, but that might divert the spending from other important areas like ICU care or other genetic disease programs. These issues should be considered before policymaking.



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