Cost-benefit analysis of a national thalassaemia prevention programme in Israel

G Ginsberg, T Tulchinsky, D Filon, A Goldfarb, L Abramov, E A Rachmilevitz

Abstract

***Objective*—In Israel (population 5.7 million) there are around 200 known living subjects with thalassaemia major, of whom around 80% are from the northern district. This study aims at examining the costs and benefits of a national screening programme to prevent thalassaemia in Israel.**

***Measurements and main results*—The lifetime healthcare costs of caring for a person born with thalassaemia major are $284 154. The costs of the home infusion service (33.1%) actually exceed the costs of the chelating agent itself (22.1%). The remaining 44.8% of costs are due to stay in hospital, operations, outpatient visits, laboratory tests, therapists, etc. Lost earnings and premature mortality costs account for a further $51 843 and $141 944 respectively for each case. A national screening programme would cost $900 197 and prevent around 13.4 homozygotes being born, at a cost of $67 369 for each birth prevented. The benefit-cost ratio of the programme to the health services is 4.22:1, which increases to 6.01:1 when a societal perspective is taken. However, around 13.0 homozygote births are still expected to occur, the majority owing to lack of compliance of patients at various stages in the screening process. The addition of a national health education programme for the higher risk non-Jewish population either nationally or in selected regions will incur extra costs, which may be covered by increased benefits as a result of better compliance with the screening programme.**

***Conclusion*—Israel should start to provide a nationwide thalassaemia screening programme as the monetary benefits to society (and even to the health services alone) will exceed the screening programmes costs.**

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β Thalassaemia major (henceforth referred to just as thalassaemia) is a fatal genetic haemolytic anaemia. Treatment regimens, using blood transfusions and chelating agents to reduce iron overload and haemochromatosis, enable patients to survive into their 20s and even 30s. Costs of the main chelating agent, desferrioxamine (Desferal, Ciba, UK), in particular,[1 2] and thalassaemia care, in general,[3–6] are expensive. Lifetime costs in 1987 based on 20–35 years' life expectancy were between £85 500 and £120 000 in the United Kingdom,[4–6] around half of which was for Desferal. As the disease is severe and treatment is difficult and expensive, programmes for secondary prevention by maternal screening and prenatal diagnosis are essential.[3]

Thalassaemia can be prevented in whole populations by a programme of community education, population screening, genetic counselling, and the offer of prenatal diagnosis.[7] Advances in preventive approaches to this disease over the past two decades have dramatically reduced the rate of new cases of thalassaemia in Sardinia,[8–12] Cyprus,[1 12 13] Greece,[14] The United Kingdom,[15–18] Canada,[17 19 20] and Italy.[21] The WHO recognises the public health importance of thalassaemia, recommending the adoption of demonstrably successful preventive approaches in other member states.[10 19]

Genetic counselling provided after the birth of the first affected child has little effect on numbers of thalassaemia cases,[5] saving a recurrence of a thalassaemic birth, but depriving parents of the chance of having at least one other healthy child.

In contrast, diagnosis made before couples enter pregnancy can identify in advance all couples at risk because of the carrier status of both potential parents, enabling them to make an informed choice about whether to undertake a pregnancy or request a prenatal diagnosis.[5]

Screening and counselling need to be extended from hospital settings into the community as it is preferable to undertake carrier screening on subjects before rather than during pregnancy. In subpopulations with a high incidence of thalassaemia it may be more efficient and economical to screen couples before marriage, relatives of subjects with thalassaemia,[12] or even school children.[11 12] Educational programmes should be aimed at school leavers, in addition to relying on massive publicity campaigns to encourage women to be screened early in pregnancy.[10 11]

THALASSAEMIA IN ISRAEL

In Israel (population 5.7 million in 1996) there are around 200 known living subjects with β thalassaemia major, of whom around 80% live in the northern district.[22] In the 1970s and 1980s 19.3 and 19.9 people were born annually with thalassaemia. Data from the 1990s show there are still around 20 thalassaemic births annually despite the introduction of some prenatal diagnosis programmes.[23]

Carriership of thalassaemia in the total Israeli population is 1–3%.[24–26] The first major

population group which has endemic thalassaemia is the non-Jewish population, especially among Bedouins and Arabs of Moslem as opposed to those of the Christian faith.[25] As a direct consequence of differences in consanguinity rates, thalassaemia prevalence varies considerably between clans in the Arab population.[27]

Jews of eastern origin are the second major group with endemic thalassaemia, especially the Kurdish Jews,[24 28–39] who have a gene carrying frequency of around 20%[25] and a mutation rate (from β globin chromosome analysis) of 240/100 000,[25] and also the Jews of Moroccan, Iraqi, and Syrian origin.[37]

In the past decade great progress has been made in clinical treatment and prenatal diagnosis of thalassaemia among both Arab and Jewish Israeli populations.[32 34] However, programmes promoting prenatal diagnosis, including genetic counselling,[40] are operated only on a limited geographic basis in some northern subdistricts. In these subdistricts, blood samples of all pregnancies are tested for haemoglobin levels, red blood cell count, and mean corpuscular volume. Samples with abnormal values are automatically sent for electrophoresis. If the person is identified as a carrier, their partner is requested to provide a blood sample for electrophoresis. If the partner's electrophoresis is also positive then both carriers enter the process and are given genetic counselling. A programme in the Hadera subdistrict also included tracing families of carriers.

In 1994 prenatal diagnosis was supplemented with educational programmes in the non-Jewish towns and villages of the Jezreel Valley and Nazareth subdistricts. These extensive educational programmes, operating from schools, community centres, and mosques, were aimed at overcoming the social and cultural practices that increase the risk of a homozygous genetic situation for thalassaemia. These practices include high rates of intermarriage within family groups,[41] a slow increase in compliance with screening and follow up, and reluctance to consider termination of pregnancy even when the prenatal diagnosis confirms that the fetus has thalassaemia major.

Cost-benefit analyses in the UK,[3 12] Sardinia,[42] Greece,[12] and Canada[19] have repeatedly shown that the costs of a nationwide thalassaemia prevention programme based on prenatal diagnosis are trivial when compared with the benefits of reducing treatment costs. This paper aims at carrying out a cost-benefit analysis of combined educational and national prenatal screening programmes for thalassaemia in Israel.

Methods

Data on costs of caring for thalassaemia homozygotes were based on the practice protocols used in the Sharai Zedek Medical Center and Hadassah-Ein Kerem University Hospitals in Jerusalem. Costs of treatment and drugs were converted to January 1996 values using a 5% annual discount rate over an assumed life expectancy of 30 years, based on the midpoint of a 25–35 year estimate of life expectancy of subjects with thalassaemia.[5 7 43] Work losses were based on an observation that only around 10% of subjects with thalassaemia are employed and that the gross national product of $15 553 per head in 1996 and average hourly wage costs per working man and woman of $16.73 and $9.89 respectively in 1995, will increase by 1% per annum.

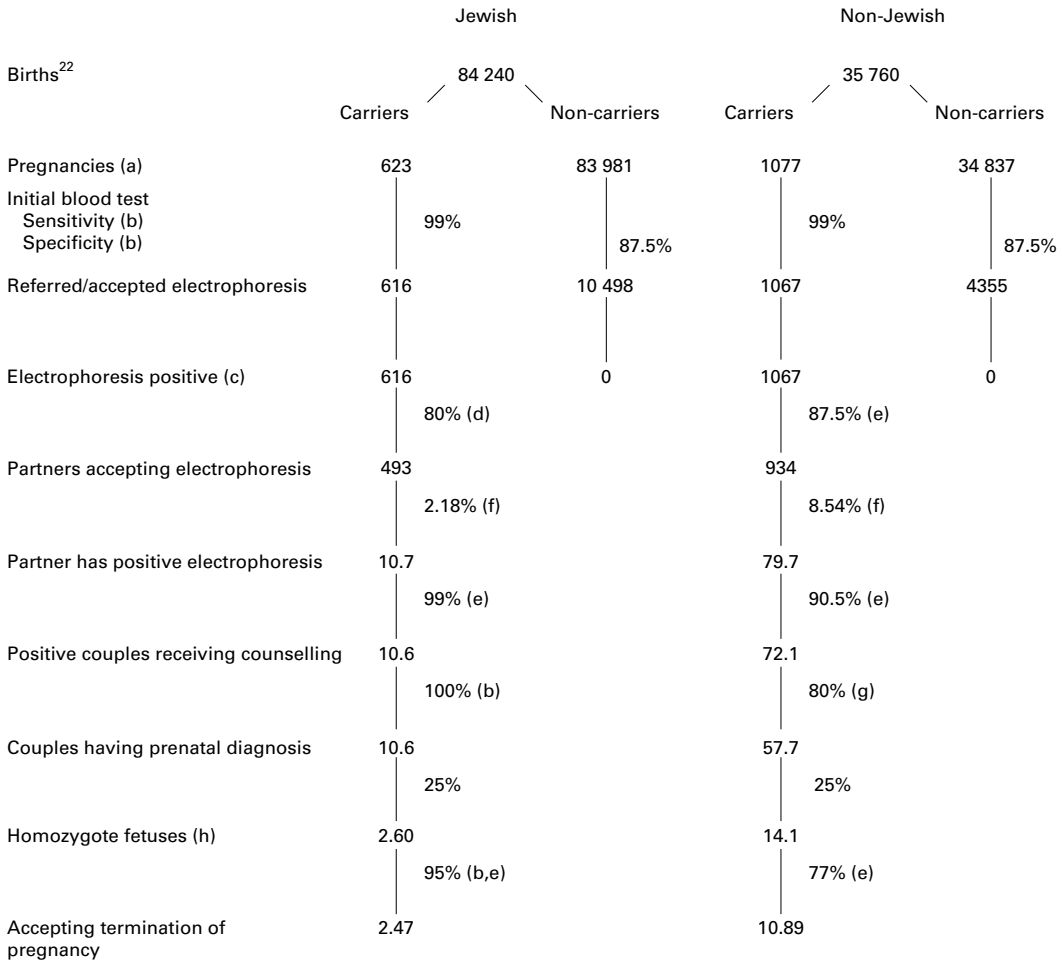
Mortality costs were estimated for these premature deaths using the gross national product per head method of valuing life, which assigns an equal value to everyone in society equivalent to the gross national product per head of the population. Everyone, whether a professor, doctor, cook, farmer, soldier, child, housewife, pensioner, unemployed, diabetic or thalassaemic homozygote receives the same valuation, based on discounting the value of the deceased's expected years of life lost.[44]

Calculations of carrier rates and subjects involved at each stage of the screening programme (fig 1) were based on data from the Jezreel Valley programme, the Central Bureau of Statistics,[22] the national diagnostic centre for thalassaemia based in Jerusalem's Hadassah Hospital, and the national thalassaemia registry based in Sheba Hospital. Estimates from the Jezreel programme of the percentage of carrier couples having prenatal diagnosis were around 100% among Jews and 57.9% among Arabs in the first years of the programme, rising to 100% in 1996–97. This compares with rates of 50%, 75%, and 90% reported from California,[45] Montreal,[20] and London, UK.[46] Our baseline model assumed a 100% prenatal diagnosis compliancy among Jews and 80% among Arabs, reflecting the effect of increased compliancy in later years of a programme. In addition, we assumed that in 80% of all cases an aborted homozygote will be replaced on average three years later by a non-homozygotic child.

Marginal additional costs of initial blood counts (actual cost around $20) to screen for thalassaemia were assumed to be zero as the practice of taking routine blood counts was started over 20 years ago in the mother and child health centres in order to screen for iron deficient anaemia during pregnancy.[47]

Identification for referral for electrophoresis screening was assumed to be made on the basis of haematological variables as used in the current Jezreel Valley study—that is, raised haemoglobin concentration ≥ 95 g/l and/or red blood cell count $\geq 4500\times10^9$/l and/or low mean cell volume <75 fl.

Electrophoresis costs were obtained from the Ministry of Health laboratory test price list. Laboratory costs were based on estimates from Hadassah Hospital taking into account economies of size that will be realised on the implementation of a larger scale thalassaemia detection programme than at present. Genetics counselling, abortion and miscarriage costs are based on updates (to January 1996) of counselling time and unit costs used in a recent cost-benefit analysis of a nationwide cystic fibrosis screening programme.[48]



Notes:
(a) Based on 120 000 live births, adjusted for multiple pregnancies[22] and a natural miscarriage rate from 16 weeks to term of 1.5%. Carrier rates based on gene frequency rates[25] and assuming a 3% carrier rate among non-Jews and an overall 1.25% carrier rate in the total population.[24–26]
(b) Estimates from the National Diagnostic Centre for Thalassaemia, Hadassah Hospital.
(c) Calculated from heterozygote carrier rates multiplied by subjects screened by ethnic group, adjusted for false negative blood tests.
(d) Based on the estimated number of parents who would refuse to take the test. as they would not abort owing to orthodox religious beliefs.
(e) Data from Jezreel Valley study.
(f) Based on rates found in the Jezreel study, adjusted by the ratio of carriers by ethnic group nationally to that found in the Jezreel Valley.
(g) Estimate based on 57.9% in initial years and 100% in past two years of the Jezreel Valley programme.
(h) Only includes true positive fetuses; 0.05 false negative Jewish fetuses and 0.29 false negative non-Jewish fetuses are excluded.

Figure 1 Screening process for thalassaemia in cohort of 120 000 births in Israel.

Finally, an additional annual cost of $70 000 was included to cover one position for a centrally based national coordinator/evaluator of thalassaemia programmes with special responsibility for Kurdish Jews.

The cost for each case averted is calculated by dividing the costs of the screening programme by the number of homozygote births averted, whether by abortion or by miscarriage (in 1.2% of the cases) as a result of the chorionic villus sampling.[49]

The basic formula used is:

Benefit-cost ratio = benefits of programme/costs of programme

where costs of programme = costs of educational programme + costs of screening; benefits of programme = average lifetime cost of treating homozygotes × number of homozygote births prevented.

Two different benefit-cost ratios were calculated using a 5.0% a year discount rate: firstly, the direct benefit-cost ratio, which only includes costs and benefits relating to health services (for example, costs of laboratory tests, ambulatory care, stay in hospital etc) and, secondly, the societal total benefit-cost ratio. This includes the direct costs and benefits in addition to indirect costs and benefits, which relate to work losses of parent and patient because of thalassaemia and benefits related to the reduction in mortality that will be achieved by implementing the programme.

Table 1 Costs of screening for β thalassaemia

	Unit cost ($)	*Numbers*	*Total cost ($)*
Initial blood test	0	120 518	0
Electrophoresis	41	16 535	685 307
Counselling for electrophoresis positives	11	1 683	18 612
Electrophoresis for partner	41	1 427	59 140
Counselling for positive couples who refused	7	22	163
Counselling for positive couples	44	82.8	3 661
Prenatal diagnosis	747	68.3	51 035
Counselling for detected negative fetus	33	51.6	1 712
Counselling for positive prenatal diagnosis	66	16.7	1 111
Miscarriage from CVS*	558	0.3	191
Termination of pregnancy	693	13.4	9 265
Total screening costs			830 197
Cost of national coordinator			70 000
Total programme costs			900 197

* CVS = chorionic villus sampling.

The array of demographic (birth rates), epidemiological (thalassaemia prevalence), health service (type and amount of care required for homozygote subjects), and economic (costs of care, tests, and genetics counselling) data were entered into a computerised spreadsheet model.

Results

The lifetime healthcare costs of caring for a person born with thalassaemia amount to $284 154. The costs of the home infusion service (used by around one third of the patients) are $93 936 (33.1%), which actually exceeds the $62 837 costs of the Desferal itself (22.1%). The remaining 44.8% of costs are due to stay in hospital, operations, outpatient visits, laboratory tests, therapists, etc. Lost earnings and premature mortality account for a further $51 843 and $68 873 respectively.

Table 1 shows the number of people and costs of each stage of a nationwide programme of screening for thalassaemia based on applying the baseline parameters (fig 1) to an estimated number of 120 518 pregnancies in 1996, an estimated 120 000 live births, adjusted for multiple pregnancies,[22] and a natural miscarriage rate from 16 weeks to term of 1.5%.

For a total cost of $900 197 around 13.4 fewer homozygotes will be born at a cost of $67 369 per birth prevented.

Since the averted excess lifetime costs of having 13.4 fewer thalassaemia major cases amount to $3.8 million to the health services and $5.4 million to society, the benefit-cost ratios were 4.22/1 and 6.01/1 respectively.

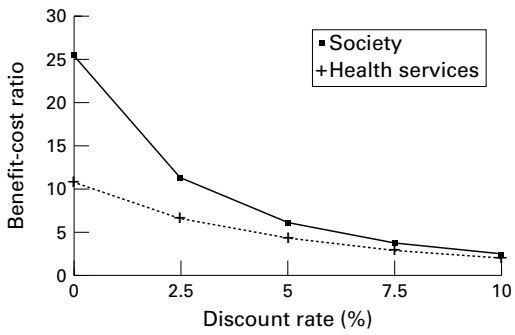


Figure 2 Benefit-cost ratios of thalassaemia screening by discount rate.

In the absence of screening we expect there to be around 26.4 thalassaemia major births in the annual cohort of 120 000 newborns. However, despite the programme, around 13.0 homozygote births are still expected to occur. The 12.1 expected homozygote births among non-Jews are due to couples refusing prenatal diagnosis (3.6), refusing to abort (3.3), partner refusing electrophoresis (2.8), positive couples refusing counselling (1.9), false negatives from chorionic villus sampling (0.3), and false negatives from initial blood tests (0.2). The main causes of the 0.9 births expected among Jews were refusal of partners to accept electrophoresis (0.67) and refusing to abort (0.13).

SENSITIVITY ANALYSES

Owing to the chronic nature of thalassaemia, the results were sensitive to changes in the discount rate (fig 2). An increase in the discount rate to 10% would decrease the benefit-cost ratio to the health services to 1.99/1. A zero discount rate, reflecting the view that morbidity in the future should not be discounted, would raise the benefit-cost ratio to the health services to 10.6/1. The internal rate of return of the programme to society is 17.0% per annum, representing the discount rate at which benefits are exactly equal to costs.

Electrophoresis costs would have to rise from $41 to $204 or to $292 in order to attain the break-even points to the health services and society respectively, where the costs of the programme just equal the benefits.

The addition of a national health education programme in the non-Jewish sector would cost an additional $359 000, based on the current Jezreel Valley and Nazareth programmes' cost of around $10 per birth per year. Therefore the total programme costs will be around $1.2 million. The educational programme would only have to prevent the birth of one extra homozygote a year to pay for itself. If the programme managed to decrease the number of non-cooperators at each stage of the counselling process by 50%, then an additional 5.3 homozygote births would be prevented, making 18.7 prevented in total at a cost of $68 429 per birth prevented. The incremental benefit-cost ratios (that is, benefits from 5.3 fewer homozygotes being born/additional cost of the educational programme) of the additional educational programme are 4.3:1 and

6.01:1 for the health services and society respectively.

If the programme increases compliancy rates among non-Jews whose partners had a positive electrophoresis to those levels currently achieved among Jews (only 1% refusing counselling, 100% of those counselled agreeing to a prenatal diagnosis and 95% aborting a homozygote fetus), then 18.4 non-Jewish homozygote births will be prevented in a total of 20.8 births prevented nationally (79% of all homozygote fetuses) at a cost of $61 490 per birth prevented.

Discussion

In the advent of a national screening programme for thalassaemia, the total costs of screening ($900 197) plus the direct lifetime medical care costs of those 13.0 homozygotes who would still be born ($3.7 million) amount to $4.6 million. If no screening programme is instituted (and present pilot programmes discontinued), around 26.4 homozygotes would be born with total lifetime medical care costs of $7.5 million. Therefore institution of a screening programme will save around $2.9 million in direct costs to the health services.

The analysis is conservative in the sense that it has not included any costs for bone marrow transplants, which may in the future become a preferred treatment for subjects with thalassaemia, with around 75% having long term survival free from disease.[50 51] However, as an alternative treatment exists for thalassaemia, bone marrow transplants must be considered very carefully owing to their attendant mortality, even if an optimal donor is available.[52] Another cause of downward bias is the (probably erroneous) implicit assumption that the health educational activities will not have any further effect on improving compliancy with the programme.

On the other hand, our estimates of benefits will be seen to be upwardly biased if the results of clinical trials enable the lower cost oral iron chelating agent, deferiprone (L1, Lipomed AG, Switzerland) to be substituted for the more expensive intravenously administered Desferal[53] and its attendant high home infusion service costs.

Extending educational programmes nationally to the whole non-Jewish population may possibly increase compliance and enable the educational programme to pay for itself. A further option is to institute regional education programmes covering the higher risk non-Jewish population of the six (out of 14) regions of Israel with the largest number of births among non-Jews, accounting for 83.6% of all non-Jewish births in Israel. The additional cost of this programme of $291 000 would be more than covered if one fewer homozygote was born each year.

In common with previous analyses, our calculations show that prevention is cheaper than care. However, care and prevention are not alternatives, they are complementary aspects of medical help for a family with a genetic problem.[4] Prevention by genetic screening can be considered as being preferred not just because of cheapness but because it also allows people choice.[4] Using "cost per affected birth prevented" as an outcome measure has been considered to be an inferior objective than using a measure of cost per "continuation of wanted (usually unaffected) pregnancies".[4 5]

Secondary benefits of screening are informed choice on the part of couples at risk[5] and the provision of reassurance to non-carriers. In addition, even though they do not plan to terminate pregnancy, some carrier parents still elect to undergo prenatal diagnosis as this allows the family to prepare emotionally and medically for the birth of a potentially affected infant.[45]

There has been a great success in preventing thalassaemia births by 96% in Cyprus, 62% in Italy, and 52% in Greece from 1972 to 1984.[54] However, births were still found to occur owing to patients' ignorance (55%), obstetricians' ignorance (26%), refusal of fetal diagnosis (9%), refusal of abortion (1%), and laboratory errors (9%).[54] In Israel our results showed that refusal of patients at various stages accounts for most of the homozygote births.

In addition, the success of our programme is also dependent on the awareness that doctors place on interpreting the result of the initial blood count. Both these reasons point to the importance of educational campaigns aimed not only at schoolchildren and prospective parents but also at members of the medical profession. Perhaps laboratory printouts of simple blood counts might be programmed to include a printed warning guide to doctors when measured levels indicate the possibility of thalassaemia and the need for electrophoresis.

Despite the moderate benefit-cost ratios of a nationwide screening programme in Israel, such a mass screening approach is relatively costly.[55] However, trying to screen on the basis of defined ethnic risk groups within the Jewish population will become less powerful as times go by, owing to rising trends of intermarriage across ethnic groups in Israel as in the United States.[56] An approach based on regions at risk, with emphasis on tracing families of carriers (even if they are outside the selected regions) might be the most cost effective approach to screening for thalassaemia. By directing screening efforts towards families of known carriers,[57] thalassaemia births were reduced by 90% in Sardinia.[10 11] A sensitivity analysis showed that applying the Israeli programme to all the Jewish Kurdish population and all the six regions with the highest absolute number of non-Jewish births gave higher benefit-cost ratios than a national programme.

In Israel, screening compulsory military service recruits at the age of 18 would leave out most of the high risk Arab groups (except some Bedouins and Druze). Such a programme would cost around $1.72 million a year, far in excess of a national prenatal screening programme including health education. Over 91% of the programme's cost is due to the initial collection and analysis of blood samples of the recruits. In any case, screening of new army recruits can be less than fully successful as examinees are rarely in a frame of mind to

absorb and use the information.[12] We estimate that the programme should discover around 75 heterozygote carriers, this is of the same order after adjusting for population increases as the 57 heterozygotes found in an army screening programme over a 12 month period in 1984–85.[37] Cost per heterozygote case detected is around $22 779.

No screening programme has ever been shown to modify marriage patterns,[12] with the exception of matchmakers within some ultra-orthodox Jewish communities in Israel and the USA who did not arrange matches between carriers of cystic fibrosis or Tay-Sachs disease.[48] Therefore, screening for thalassaemia carriers could also concurrently be carried out in ultra-orthodox communities.

Israel has established successful programmes for screening for other congenital diseases, including phenylketonuria and Tay-Sachs disease. Israel also operates a nationwide programme of mother and child health centres, so that it should be possible to organise a national screening programme for thalassaemia. The data from the present study suggest that clinical and public health authorities should act and invest in a similar national programme for prevention of thalassaemia based on health education and screening activities, which could change the pattern of this disease within a short number of years.

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3rd Asia-Pacific Regional Meeting of the International Society for Neonatal Screening

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The meeting, with the theme "Neonatal screening in the 21st century", will provide a forum for discussion of advances in neonatal screening, metabolic disorders, and common neonatal disorders in the region. The scientific programme will cover both basic science and clinical applications.

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