ANNEX 3A. An Essential Package of Interventions to Address Congenital and Genetic Disorders

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INTRODUCTION

Congenital disorders can be defined as conditions that are present before or at the time of birth. They may be acquired *in utero*, following maternal exposure to a pathogen or toxic substance, or they may be inherited through genes. The latter subset of genetic disorders, in turn, may arise from single gene defects (such as in those encoding hemoglobin production), chromosomal abnormalities (such as in Down syndrome), or more complex defects or gene-environment interactions (such as in cleft lip and palate). These conditions are usually identified at birth or early in life, with varying but significant levels of lifelong disability and excess risk of mortality.

Congenital and genetic disorders are not often prioritized in global and national health policies. For one, they are considered noncommunicable diseases that often do not have simple cures that can be scaled through targeted programs. In addition, while this group of conditions is collectively important in terms of global disease burden, individual disorders are often rare. Nevertheless, with widespread reductions in under-five mortality, there will likely be greater pressure on public health systems in low- and middle-income countries to begin incorporating care for children with these disorders.

Disease Control Priorities, 2nd Edition (*DCP2*) contained several chapters that dealt with congenital and genetic disorders to varying degrees. For instance, chapter 34 dealt exclusively with inherited disorders of hemoglobin, and chapter 49 covered a variety of developmental disabilities. Disease Control Priorities, 3rd Edition (*DCP3*) has also addressed these disorders in a few places. For example, management of cleft palate and club foot are discussed in Volume 1 (Essential Surgery), and congenital heart disease is discussed in Volume 5 (Cardiovascular, Respiratory, and Related Disorders). The objective of this Annex is to provide a balanced discussion on congenital and genetic disorders, building on the recommendations from *DCP2*, and addressing important conditions that have not been covered elsewhere in *DCP3*.

DISEASE BURDEN

According to the WHO Global Health Estimates 2015, congenital anomalies accounted for 650,000 deaths and 65 million disability-adjusted life-years (DALYs) in 2015, or 1.1% of total deaths and 2.4% of total DALYs (1). The most frequent cause of deaths and DALYs was congenital heart disease (300,000 deaths and 28 million DALYs), with the residual category "other congenital anomalies" being the second most frequent (230,000 deaths and 25 million DALYs). Down syndrome and other chromosomal abnormalities were disproportionately

important as causes of DALYs (5.7 million in total) relative to deaths (50,000 in total), indicating high levels of nonfatal disability from these disorders.

Most deaths from congenital disorders occur before the age of five, with a slight male predominance at younger ages (Figure 3A.1). Unfortunately, detailed estimates of nonfatal outcomes from specific disorders is often lacking. Wide ranges of incidence and prevalence estimates are often reported because of regional genetic variations. A classic example of such variation is in disorders of hemoglobin (i.e., sickle cell disease and thalassemia). The Global Burden of Disease 2015 study estimated that the prevalence of sickle cell disease ranged from one per 100,000 in Canada to 700 per 100,000 in Burkina Faso. Similarly, the prevalence of thalassemia ranged from 0.003 per 100,000 in Portugal to 80 per 100,000 in Thailand (2).

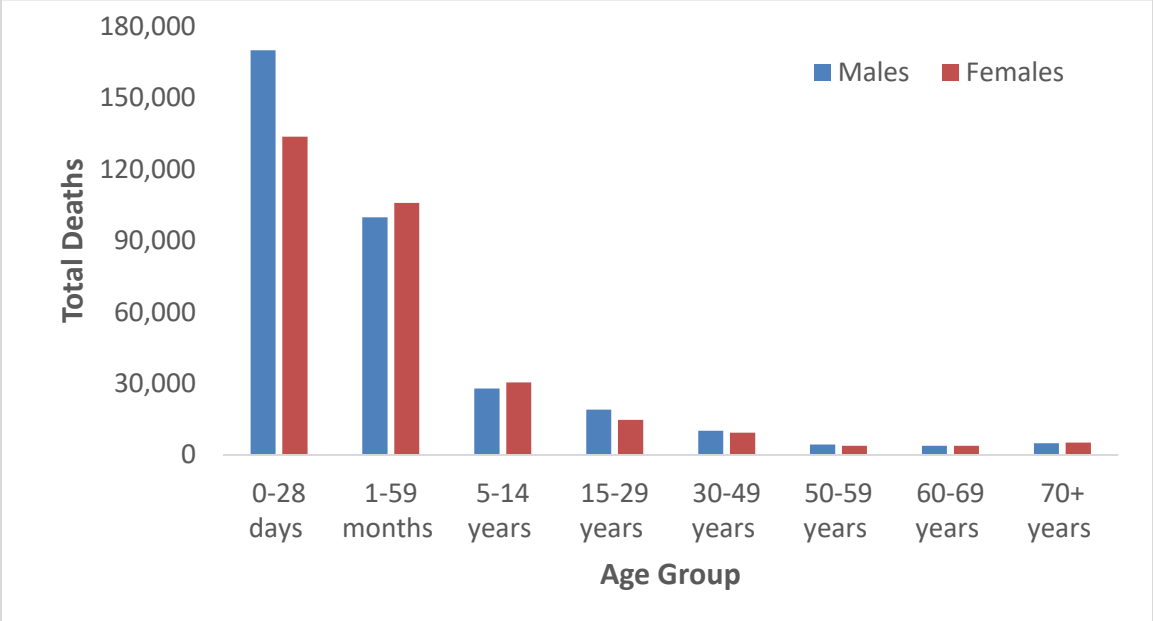

Figure 3A.1 Global deaths from congenital anomalies by age and sex in 2015

Many genetic disorders are especially prevalent in regions of the world where consanguinity is common, including North Africa, the Middle East, and South Asia. Consanguinity raises the risk of genetic disorders, many of which have an autosomal recessive pattern of inheritance that leads to clustering in families. The prevalence of certain genetic disorders has noticeably declined in settings where preconception screening and counseling of carriers has become routine, such as in the case of thalassemia in Cyprus (3).

IDENTIFICATION OF EFFECTIVE INTERVENTIONS

The authors reviewed relevant chapters in *DCP2*, scientific literature, and technical guidelines promulgated by WHO to identify interventions for congenital and genetic disorders. For the purpose of inclusion in the essential package presented below, interventions had to have three characteristics: (1) good value for money (usually measured in cost-effectiveness), (2) addressed a significant disease burden, and (3) feasible to implement in low- and middle-income countries.

Table 3A.1 summarizes conditions and interventions that were considered for inclusion in the essential package.

Table 3A.1 Candidate interventions for the essential package for congenital and genetic disorders

Interventions during preconception period	**Target**
Food fortification: iodized salt	Iodine deficiency: mental retardation, cretinism
Food fortification: flour folic acid, B12	Neural tube defects; other malformations
Staple food fortification: flour or rice; iron	Maternal anaemia, neurodevelopmental delay
Screening for carriers of common recessive disorders: thalassemia, sickle cell disorders, selected metabolic disorders	Selected metabolic and single-gene disorders
Immunization: rubella	Congenital rubella syndrome
Immunisation: hepatitis B	Maternal/congenital hepatitis B infection
Screening and treatment of infections: syphilis, HIV/AIDS, others	Congenital infection
Screening, diagnosis and glycemic control	Decrease in congenital malformations
Triage, assessing genetic family history, referral of high risk families	Varies
Blood grouping (ABO, rhesus)	Rhesus hemolytic disease of the newborn
Maternal age information	Miscarriage, chromosomal disorders
Interventions during pregnancy	**Target**
Management of maternal conditions - diabetes, epilepsy, hypertension	Disorder-related increment in congenital malformations
Screening and treatment of infections	Principally, congenital syphilis and toxoplasmosis
Prenatal screening: 1st trimester maternal serum markers and ultrasound, with prenatal diagnosis and option of termination	Chromosomal disorders, major congenital malformation
Fetal anomaly ultrasound scan, with/without option of termination	Congenital malformations
Prenatal diagnosis of single gene disorders, with option of termination	Single gene disorders
Dietary supplement - iron, folate, multivitamins	Maternal dietary deficiency leading to neural tube defects; other malformations
Interventions after birth	**Target**
Newborn biochemical screening for common congenital disorders: hypothyroidism, PKU, sickle cell disorders, G6PD deficiency	Selected metabolic and single-gene disorders
Newborn screening for hearing impairment, congenital hip dislocation, clinically identifiable congenital disorders	Identifiable causes of disability
Management: general newborn management of identified conditions and pediatric surgery to correct malformations	Selected anatomic disorders
Genetic risk identified: extended family screening, testing and counseling	Single gene disorders

Note: interventions included in other essential packages are shown in green.

REVIEW OF ECONOMIC EVIDENCE

The authors also sought to identify which interventions in Table 3A.1 had economic evidence supporting their implementation in low- and middle-income countries. A structured literature review was conducted using Medline (Table 3A.2). The search was limited to the January 1,

2000 to the present and to English-language studies with abstracts available. Studies were included if they reported cost-effectiveness or benefit-cost ratios comparing one or more interventions in typical limited-resource settings. Reviews/editorials, studies from high-income settings, and cost analyses were excluded, and studies of interventions recommended elsewhere in *DCP3* (i.e., the green interventions in Table 3A.1) were not assessed further since they had already been summarized.

Table 3A.2 Medline search strategy for economic studies of congenital and genetic disorders

1. Geography term
"south America" OR "latin America" OR afghanistan OR albania OR algeria OR angola OR argentina OR armenia OR armenian OR azerbaijan OR bangladesh OR benin OR belize OR bhutan OR bolivia OR botswana OR brazil OR "Burkina Faso" OR burundi OR cambodia OR "Khmer Republic" OR kampuchea OR cameroon OR cameroons OR cameron OR cameron OR "Cape Verde" OR "Central African Republic" OR chad OR china OR colombia OR comoros OR comoro islands OR comores OR mayotte OR congo OR zaire OR "Costa Rica" OR "Cote d'Ivoire" OR "Ivory Coast" OR djibouti OR "French Somaliland" OR dominica OR "Dominican Republic" OR "East Timor" OR "East Timur" OR "Timor Leste" OR ecuador OR egypt OR "United Arab Republic" OR "El Salvador" OR eritrea OR ethiopia OR fiji OR gabon OR "Gabonese Republic" OR gambia OR gaza OR georgia OR ghana OR grenada OR guatemala OR guinea OR guiana OR guyana OR haiti OR honduras OR india OR maldives OR indonesia OR kenya OR kiribati OR "Lao PDR" OR laos OR lesotho OR basutoland OR liberia OR libya OR madagascar OR "Malagasy Republic" OR sabah OR sarawak OR malawi OR nyasaland OR mali OR "Marshall Islands" OR mauritania OR mauritius OR "Agalega Islands" OR mexico OR micronesia OR moldova OR moldova OR moldovan OR mongolia OR montenegro OR morocco OR ifni OR mozambique OR myanmar OR myanmar OR burma OR namibia OR nepal OR "Netherlands Antilles" OR nicaragua OR niger OR nigeria OR muscat OR pakistan OR palau OR palestine OR panama OR paraguay OR peru OR philippines OR philippines OR philippines OR philippines OR rwanda OR ruanda OR nevis OR "Saint Lucia" OR "St Lucia" OR "Saint Vincent" OR "St Vincent" OR grenadines OR samoa OR "Samoan Islands" OR "Navigator Island" OR "Navigator Islands" OR "Sao Tome" OR senegal OR serbia OR montenegro OR seychelles OR "Sierra Leone" OR "Sri Lanka" OR ceylon OR "Solomon Islands" OR somalia OR sudan OR suriname OR surinam OR swaziland OR tajikistan OR tadzhikistan OR tadjikistan OR tadzhik OR tanzania OR thailand OR togo OR "Togolese Republic" OR tonga OR tunisia OR turkey OR turkmenistan OR turkmen OR uganda OR ukraine OR vanuatu OR "New Hebrides" OR venezuela OR vietnam OR "Viet Nam" OR zambia OR zimbabwe OR "Africa, Northern" OR "Northern Africa" OR "North Africa" OR "Africa South of the Sahara" OR "sub-Saharan Africa" OR "subsaharan Africa" OR "Africa, Central" OR "central Africa" OR "Africa, Eastern" OR "Eastern Africa" OR "east Africa" OR "Africa, Southern" OR "southern Africa" OR "Africa, Western" OR "western Africa" OR "west Africa" OR "Caribbean Region" OR caribbean OR "Central America" OR "Panama Canal Zone" OR "French Guiana" OR borneo OR "Mekong Valley" OR "mekong delta" OR "Republic of Congo" OR congo-brazzaville OR "Democratic Republic of the Congo" OR DRC OR congo kinshasa OR "South Sudan" OR "South Africa" OR guinea-bissau OR Africa OR developing countr*[All Fields] OR low and middle-income countr*[All Fields] OR LMIC[All Fields]
2. Economics term
cost-effective*[All Fields] OR cost-benefit[All Fields] OR cost-utility[All Fields] OR econom*[All Fields]
3. Health condition term
"Neonatal screening"[All Fields] OR "Newborn screening"[All Fields] OR "Prenatal screening"[All Fields] OR Prenatal diagn*[All Fields] OR "Congenital, Hereditary, and Neonatal Diseases and Abnormalities"[Mesh]

This search strategy was run on April 24, 2017 and yielded 302 records. A majority of these studies dealt with hemoglobin disorders, hearing defects, and prenatal screening in general. There were a significant number of studies on antenatal screening for syphilis, which is not

included in our review below. Inborn errors of metabolism and chromosomal disorders were not covered as frequently.

During the initial search, the authors noted that many papers, though not economic in nature, described clinical experiences with newborn and prenatal screening in low- and middle-income settings. These reports found that screening programs were generally feasible, at least in pilot settings. Recurrent themes in these studies included concern over the cost of screening and cultural and ethical considerations, e.g., around termination of pregnancy or societal attitudes towards genetic diseases in general.

After reviewing titles and abstracts, full text reports were obtained for 15 studies, 11 of which were considered in the development of our essential package. Table 3A.3 presents the main findings of this review, including estimates of cost-effectiveness. (As is done throughout *DCP3*, all costs were converted and deflated to 2012 US dollars for comparability.)

Table 3A.3 Summary of economic evaluations of interventions for congenital and genetic disorders

Author/year (reference)	Location	Intervention	Comparator	Finding
Hearing loss				
Burke 2012 (4)	India	Universal newborn hearing screening (OAE followed by AABR if the first screen was positive)	Selective screening of newborns at high risk	US$ 3900 per case detected
Burke 2012 (4)	India	One-stage newborn hearing screening using OAE only	Two-stage newborn hearing screening	US$ 23,000 per additional true positive case detected
Huang 2012 (5)	China	Universal screening	Targeted screening	US$ 6800-190,000 per DALY averted depending on coverage and quality of program
Tobe 2013 (6)	China	Universal OAE and AABR	No screening	US$ 61,000 per DALY averted
Tobe 2013 (6)	China	Universal OAE	No screening	US$ 14,000 per DALY averted
Tobe 2013 (6)	China	Targeted OAE and AABR	No screening	US$ 48,000 per DALY averted
Tobe 2013 (6)	China	Targeted OAE	No screening	US$ 4900 per DALY averted
Hemoglobinopathies				
Ahmadnezhad 2012 (7)	Iran	Retrospective identification of cases plus prospective (premarital) screening and counseling for thalassemias	No screening	US$ 130 per case prevented
Yang 2016 (8)	China	Prenatal ultrasound screening for alpha-thalassemia among at-risk women	Invasive screening (chorionic villus sampling or amniocentesis)	Cost saving
Kuznik 2016	Sub-	Universal newborn screening	No screening	US$ 120-11,000 per

(9)	Saharan African countries	for sickle cell disease followed by prophylaxis against bacterial infections and malaria*		DALY averted depending on SCD incidence (probably very cost-effective in 34 countries)
McGann 2015 (10)	Angola	Newborn screening for sickle cell disease followed by prophylaxis**	No screening	$41 per healthy life-year gained
Inborn errors of metabolism				
Camelo 2009 (11)	Brazil	Addition of galactosemia screening to existing neonatal program	Existing neonatal program	BCR 1.0 (0.35-2.8)
Sladkevicius 2010 (12)	Libya	Neonatal screening for phenylketonuria alone	No screening	Cost-saving; 90% ROI
Thiboonboon 2015 (13)	Thailand	Screening for phenylketonuria, isovaleric academia, methylmalonic academia, propionic acidemia, maple syrup urine disease, and multiple carboxylase deficiency	Screening for phenylketonuria alone	$87,000 per QALY gained
Other congenital and genetic disorders				
Chen 2007 (14)	China	Prenatal diagnosis of Down syndrome using chorionic villus sampling or amniocentesis among females 35+ years	No screening	US$ 23,000 per case prevented
Chen 2007 (14)	China	Prenatal diagnosis od Down syndrome using serum AFP and hCG testing	No screening	US$ 97,000 per case prevented

Note: interventions that had good value for money at typical low- and lower-middle-income country levels of willingness to pay are shown in red. OAE = otoacoustic emission; AABR = automated auditory brainstem response; SCD = sickle cell disease; hCG = human chorionic gonadotropin

Three studies addressed congenital hearing loss screening among infants. In general, selective or targeted screening efforts were more cost-effective than universal screening. (Selective screening in these settings was based on the presence of risk factors including family history of hearing impairment or craniofacial anomalies.) In addition, otoacoustic emission was found to be a more cost-effective method than automated auditory brainstem response.

It is also worth noting that, with hearing screening as well as other congenital disabilities, the presence of adequate rehabilitative services (including hearing assistive devices, speech pathology services, etc.) was a key factor in these studies and would be a necessary element for beginning a hearing screening program in a low-resource setting.

Four studies assessed disorders of hemoglobin in African and Asian settings. Two studies assessed screening for thalassemias. and two studies assessed screening and care for sickle cell disease. Screening for beta thalassemia was found to cost-effective using a pre-conception

approach (i.e., that resulted in cancellation of marriage) in Iran; this mechanism of impact was similar to the Cyprus experience cited previously. Screening and care for sickle cell disease can be very cost-effective in African countries with a high incidence of sickle cell trait, and in fact the incremental cost-effectiveness ratio declines in proportion to the incidence rate. These screening studies generally assume a basic package of care for infants who screened positive; the package would include regular penicillin, pneumococcal vaccination, antimalarials, and bednets (replaced annually) for infection prophylaxis as well as folic acid supplementation for anemia prevention. Neither study looked at benefits beyond childhood nor potential longitudinal interventions (e.g., hydroxyurea, transfusion to prevent stroke, splenectomy, management of pain crises, etc.), a major gap in the literature.

Three studies addressed various inborn errors of metabolism, with two studies that looked at phenylketonuria (PKU), one of the more treatable disorders. The general conclusions from these studies are, firstly, that disease incidence is a major driver of cost-effectiveness or benefit-cost ratios for various screening tests, and second, that PKU appears to be common enough across low- and middle-income settings to justify its inclusion in a newborn screening package.

One study looked at screening for Down syndrome, and this study concluded that this intervention was not cost-effective because of the expense of screening and poor test performance characteristics.

The authors found no studies on another important and relatively common condition, congenital hypothyroidism. It should be noted that thyroid function tests are relatively inexpensive in most settings, and generic thyroid hormone replacement therapy is also inexpensive, though affected individuals need to take replacement therapy for years and in many cases for life. Having said this, the health benefits of screening and treatment, as compared to doing nothing, include significant and lifelong reductions in the risk of intellectual disability and potentially reductions in other cardiovascular and metabolic disorders. Hence the authors' judgment is that screening and care for congenital hypothyroidism is likely to be cost-effective in limited resource settings.

RECOMMENDATIONS

Based on the evidence above and recommendations from other areas of DCP3, the following essential package is proposed (Table 3A.4). Again, these recommendations should be interpreted in light of local incidence data for various disorders and the capacity to provide healthcare (including referral care in some cases). The authors recommend that, at least in the short- to medium-term in low- and lower-middle-income countries, newborn screening be conducted at outpatient departments of first-level hospitals, which are in a better position both to manage the volume of pathology services and to coordinate care for individuals who screen positive. As resources permit, screening could be devolved to community settings, and in the case of inborn errors of metabolism, the battery of disorders tested for could be expanded.

Table 3A.4 Essential package of interventions for congenital and genetic disorders in low- and middle-income countries

Intersectoral policies	Population-based health services	Community	Health centers	First-level hospitals	Referral and specialty hospitals
1. Fortification of food products with folate and iron		3. EPI vaccination series (diptheria, pertussis, tetanus, polio, BCG, measles, hepatitis B, Hib, and rubella)	5. PMTCT of HIV (Option B+) and syphilis	8. Targeted screening for congenital hearing loss in high-risk children* using otoacoustic emissions testing	12. Repair of cleft lip and palate
2. Iodization of salt		4. IEC on folic acid and iron supplementation (all women of reproductive age)	6. Screening and management of diabetes in pregnancy (gestational diabetes or preexisting Type 2 diabetes)	9. Universal newborn screening for congenital endocrine or metabolic disorders (e.g., congenital hypothyroidism, phenylketonuria) that have high incidence rates and for which long-term treatment is feasible in limited resource settings	13. Repair of club foot
			7. Folic acid and iron supplementation for all pregnant women	10. In settings where sickle cell disease is a public health concern, universal newborn screening followed by standard prophylaxis against bacterial infections and malaria	
				11. In settings where specific single-gene disorders are a public health concern (e.g., thalassemias), retrospective identification of carriers plus prospective (premarital) screening and counseling to reduce rates of conception	

Notes: The first-level hospital platform includes outpatient specialist care and routine pathology services (e.g., newborn screening) that cannot be feasibly delivered at lower levels.
* High-risk individuals are those who either have craniofacial abnormalities at birth or who have a family history of hearing impairment.

REFERENCES

1. WHO. Global Health Estimates (GHE). Geneva: World Health Organization; 2017.
2. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 acute and chronic diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388:1545-602.
3. Bozkurt G. Results from the north cyprus thalassemia prevention program. Hemoglobin. 2007;31(2):257-64.
4. Burke MJ, Shenton RC, Taylor MJ. The economics of screening infants at risk of hearing impairment: an international analysis. Int J Pediatr Otorhinolaryngol. 2012;76(2):212-8.
5. Huang LH, Zhang L, Tobe RY, Qi FH, Sun L, Teng Y, et al. Cost-effectiveness analysis of neonatal hearing screening program in China: should universal screening be prioritized? BMC Health Serv Res. 2012;12:97.
6. Tobe RG, Mori R, Huang L, Xu L, Han D, Shibuya K. Cost-effectiveness analysis of a national neonatal hearing screening program in China: conditions for the scale-up. PloS one. 2013;8(1):e51990.
7. Ahmadnezhad E, Sepehrvand N, Jahani FF, Hatami S, Kargar C, Mirmohammadkhani M, et al. Evaluation and cost analysis of national health policy of thalassaemia screening in west-azerbaijan province of iran. Int J Prev Med. 2012;3(10):687-92.
8. Yang Y, Li DZ, He P. A Program on Noninvasive Prenatal Diagnosis of alpha-Thalassemia in Mainland China: A Cost-Benefit Analysis. Hemoglobin. 2016;40(4):247-9.
9. Kuznik A, Habib AG, Munube D, Lamorde M. Newborn screening and prophylactic interventions for sickle cell disease in 47 countries in sub-Saharan Africa: a cost-effectiveness analysis. BMC Health Serv Res. 2016;16:304.
10. McGann PT, Grosse SD, Santos B, de Oliveira V, Bernardino L, Kassebaum NJ, et al. A Cost-Effectiveness Analysis of a Pilot Neonatal Screening Program for Sickle Cell Anemia in the Republic of Angola. J Pediatr. 2015;167(6):1314-9.
11. Camelo JS, Jr., Fernandes MI, Maciel LM, Scrideli CA, Santos JL, Camargo AS, Jr., et al. Galactosaemia in a Brazilian population: high incidence and cost-benefit analysis. J Inherit Metab Dis. 2009;32 Suppl 1:S141-9.
12. Sladkevicius E, Pollitt RJ, Mgadmi A, Guest JF. Cost effectiveness of establishing a neonatal screening programme for phenylketonuria in Libya. Appl Health Econ Health Policy. 2010;8(6):407-20.
13. Thiboonboon K, Leelahavarong P, Wattanasirichaigoon D, Vatanavicharn N, Wasant P, Shotelersuk V, et al. An Economic Evaluation of Neonatal Screening for Inborn Errors of Metabolism Using Tandem Mass Spectrometry in Thailand. PloS one. 2015;10(8):e0134782.
14. Chen Y, Qian X, Li J, Zhang J, Chu A, Schweitzer SO. Cost-effectiveness analysis of prenatal diagnosis intervention for Down's syndrome in China. Int J Technol Assess Health Care. 2007;23(1):138-45.