Outcome without screening:
Congenital hypothyroidism is caused by inadequate production of thyroid. Babies with congenital hypothyroidism who are not identified and treated promptly have many problems and were formerly termed cretins. Characteristics of cretinism include severe mental retardation, coarse facial features, poor growth, deafness, and neurological abnormalities. Newborn screening for congenital hypothyroidism is done because affected newborns rarely show the clinical features that appear later, generally in the first year of life. Before newborn screening, congenital hypothyroidism imposed a high burden on the family and community to provide medical and institutional care of affected individuals.

Incidence:
The incidence of congenital hypothyroidism is one in 4,500 births.

Outcome with screening:
From a cost to benefit perspective, screening for congenital hypothyroidism is very successful because it identifies approximately 1,400 infants annually in the US, who with early treatment, are given the opportunity to lead healthy, normal lives.

Prompt diagnosis and treatment prevents the mental retardation and somatic abnormalities of congenital hypothyroidism. The intellectual deficiency of late-diagnosed congenital hypothyroidism has been estimated to be 5 IQ points per month of delay. Because of this progressive delay, the goal is to screen, diagnose, and treat all infants with congenital hypothyroidism within two weeks of birth. Invariably, cases will arise that are not straightforward in their presentation. For example, some infants have TSH values that are minimally elevated and normal levels of $T_4$. Some infants with undisputed congenital hypothyroidism do not show a diagnostically elevated TSH in the newborn screen, and thus go undiagnosed. Individuals with Down’s syndrome are more likely to show mild TSH elevations without clear evidence of hypothyroidism. Given the implications of hypothyroidism on the neurological and intellectual development of the child, it is important to treat such children with thyroxine until they reach three (3) years of age when the effects of thyroid hormone deprivation on the central nervous system are much reduced. At that time, thyroid hormone replacement can be discontinued and additional diagnostic studies performed. It is essential that any infant or child who manifests symptoms consistent with hypothyroidism be retested by the primary care provider regardless of the results of the newborn screen.

Causes of congenital hypothyroidism:
Congenital hypothyroidism affects 1 in 4,500 babies. The incidence may be somewhat lower in African American populations, and the incidence may be as high as 1 in 1,600 Hispanic births.

Primary hypothyroidism: The most common of congenital hypothyroidism is the complete absence of a thyroid gland, or thyroid agenesis. Since thyroid agenesis affects the thyroid gland itself it causes primary hypothyroidism. Other causes of primary congenital hypothyroidism include:
thyroid dysgenesis, or the presence of inadequate amounts of poorly functioning, often misplaced (such as on the tongue) thyroid tissue,
(2) enzyme defects in the synthesis of thyroid hormones, which are inherited in an autosomal recessive manner,
(3) abnormalities of the TSH receptor, which makes the thyroid insensitive to TSH from the pituitary gland, and
(4) iodine deficiency, which has become quite rare in the US, but is still common in regions of the world that contribute to the immigrant populations of Tennessee.

Some forms of primary congenital hypothyroidism are transient, but may require treatment of the infant for the first several months of life. Prenatal exposure of the fetus, via the mother, to excessive iodine in cough medications, contrast agents for X rays or aminography, and drugs such as amiodarone, can cause hypothyroidism. Antithyroid drugs such as propylthiouracil and methimazole, which are used to treat mothers with thyrotoxicosis can cross the placenta and cause the newborn to be hypothyroid. Finally, some mothers with autoimmune thyroid diseases such as Hashimoto Thyroiditis and Grave's Disease can impart antibodies to the fetus and affect the function of the thyroid.

Secondary hypothyroidism: These disorders are caused by deficiencies in the thyroid regulating hormone, TSH. They include infants with pituitary insufficiency, who may also have structural abnormalities in their pituitary, hypothalamus, or brain and defects in secretion of other pituitary hormones such as growth hormone, ACTH, and gonadotropins. There are also less common, genetic forms of secondary hypothyroidism in which a biologically inactive form of TSH is secreted.

Screening test and confirmation:
Newborn screening for congenital hypothyroidism in Tennessee is a primary TSH screening approach. The only measurement made on the infant’s blood sample is of TSH, and those infants who exceed the cutoff values based on age are identified to their primary care providers (PCP) for follow-up, which consists of confirmatory studies on a venous blood sample. A major factor in primary TSH screening is the normal surge in the infant’s TSH levels at birth. For the first 3-6 hours of life TSH levels dramatically rise and then decrease. Thus sampling <24 hours of life often results in values that are above the cutoff established for slightly older infants, and results in a higher rate of recall. Contemporary trends to early hospital discharge and home delivery have increased the number of samples rejected by the Newborn Screening Laboratories because of early sampling. Another physiologic variation that impacts on primary TSH screening arises in a small subset of infants with congenital hypothyroidism whose rise in TSH level is inexplicably delayed by several weeks. Very low birth weight infants may be at greater risk for this phenomenon. To identify these infants, a few states employ a mandatory second thyroid screen between 2 and 6 weeks of age; Tennessee does not, and these children could be missed in the absence of clinical vigilance on the part of the PCP.

After a child has been identified to the PCP as having a positive result in the screen, the next step is to obtain a confirmatory blood sample for T₄ and TSH by venipuncture. Other blood measurements may be warranted and a network of Pediatric Endocrinologists is available across Tennessee to assist in the evaluation and treatment of congenital hypothyroidism. Diagnosis of primary congenital hypothyroidism is based on an elevated TSH and usually, but not always, a low T₄. It is important to be aware of the fact that normal T₄ values for infants in the first weeks of life are substantially higher than for the normal adult population and for older children. Once the diagnosis is established, the PCP or endocrinologist may then embark on
studies to determine the form of hypothyroidism: 1) radionuclide scans ($^{123}$I or $^{99}$Tc) and ultrasound may be used to confirm the absence of functioning thyroid tissue, 2) skeletal radiographs are useful in determining the severity of hypothyroidism and may have some prognostic value in developmental outcome and 3) blood measurements of TSH blocking immunoglobulins (TBII) may be helpful in the rare forms of maternal thyroid autoimmunity that results in newborn hypothyroidism.

**Treatment:**
Therapy consists of thyroxine replacement at a dose adequate to promptly reduce the TSH and bring the serum $T_4$ or free $T_4$ into the upper half of the normal range for age. Thyroxine is given at 10-18 $\mu$g/kg per day. Thyroxine tablets are the standard form of replacement and suspensions of thyroxine are avoided. Tablets are available in 25, 50, and 75 $\mu$g and higher, and doses can be adjusted by using combinations of whole and half tablets. Routine serum $T_4$ and TSH are measured at two weeks, and then at monthly intervals for the first two months; two-monthly intervals until six months; three-monthly until two years, and then every six months throughout childhood. The child’s growth and development are carefully followed at each visit. Both $T_4$ and TSH should be checked. A small minority of infants will exhibit TSH values that do not come into the normal range because of an apparent resetting of their hypothalamic threshold for suppression. Typically, these infants show signs of over-treatment, irritability, increased stool frequency, and perhaps poor weight gain when attempts are made to drive the TSH into the normal range. Maintaining the free $T_4$ in the upper half of the normal range is the primary goal of treatment.

**Special concerns and issues:**
It is important to bear in mind the difference between primary and secondary causes of hypothyroidism. The physiology of these two causes and the screening methods needed for their identification are quite different. When its absence or dysfunction impairs the function of the thyroid gland, the infant's pituitary gland will attempt to compensate by secreting increased amounts of TSH. In congenital primary hypothyroidism, serum concentrations of thyroid hormones such as thyroxine ($T_4$) are typically low, and TSH is elevated. In contrast, in secondary hypothyroidism, in which the defect is not in the thyroid but in the hypothalamus or pituitary, TSH concentrations may be low or normal, while the $T_4$ is low.

Given the inherent pitfalls in thyroid screening, it is imperative that the primary care providers know and be alert to the symptoms of untreated congenital hypothyroidism and have a very low threshold to retest any infants in whom the diagnosis is suspected, regardless of the screening results. These include: a gestation >42 weeks, delayed skeletal maturity as evidenced by large fontanelles, especially the presence of a posterior fontanelle >1 cm$^2$ in area, or a delayed bone age determined by radiographs of the knee and ankle; hypothermia, cold extremities, or mottling; prolonged jaundice; poor feeding, lethargy, a hoarse cry, hypotonia, constipation or the presence of an umbilical hernia. In infants with secondary hypothyroidism, who are among the most likely to be missed by a primary TSH screen, midline facial defects such as high arched palate, wide-spaced eyes, or optic nerve hypoplasia may be a clue of hypothalamic dysfunction. These infants may experience hypoglycemia from their inability to secret ACTH or growth hormone. Growth failure in these children is often not seen until the second year of life. Boys with hypothalamic insufficiency may have underdeveloped genitalia with undescended testes.

The long-term prognosis of early-diagnosed and treated congenital hypothyroidism has been uniformly positive, but not in every instance optimal. Studies that measured the intellectual outcomes of these children have concluded that early diagnosis is a major factor in determining outcome, but other factors such as a severe bone age delay and a low initial $T_4$ value at the
time of diagnosis may identify a subset of children with congenital hypothyroidism whose IQ may be below those of their siblings or normal controls. It should be noted that the currently recommended starting doses of thyroxine are higher than those employed in the past and may help close the development gap noted by some studies in sub-populations of children with this disorder. It is accurate to inform parents that a diagnosis of congenital hypothyroidism made early, treated promptly, and monitored appropriately, will largely, if not totally, prevent long term developmental or intellectual deficits. Prompt diagnosis, appropriate therapy and monitoring, and parental compliance are the critical factors that are under our control and should be stressed in the long-term management of these children. Vigilance on the part of the clinicians to finding potentially undiagnosed cases is critical to bringing the benefits of treatment to all children with congenital hypothyroidism. In addition, PCP participation in the newly established monitoring program for children with congenital hypothyroidism will assist the Department of Health in determining the roadblocks to optimal care in the current system.

References:
AAP Section on Endocrinology and Committee on Genetics, and American Thyroid Association Committee on Public Health, *Newborn Screening for Congenital Hypothyroidism:*


Fisher, D.A. *Disorders of the Thyroid in the Newborn and Infant.* Chapter 4 In Sperling MA


Gruters, A. Congenital Hypothyroidism, Pediatric Annuals 21:15-28