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Thyroid Patents

Abstract

The thyroid is a bilobal gland located at the base of the neck and produces essential hormones for metabolic control in the human body. Affecting nearly fifty-million Americans, thyroid disease has become a ubiquitous cause for symptoms including depression, anxiety, and heart disease. Yet, while the healthcare law literature is visibly scaling, the research relating to patents for cures to thyroid diseases is completely uncharted.

As such, this article offers the first empirical review for Thyroid Patents. First, this Article discusses and explains the thyroid gland's hormonal feedback loop, common diseases, available technologies, and treatment options. Second, this Article introduces the Thyroid Patent Dataset, contributing empirical patent analysis to literature, and further providing legal claims critique and damages calculation guidelines. In short, this Article explores the thyroid gland's intersection with patent law to promote knowledge in human health and prompt innovation for biotechnology.

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Introduction

Thyroid Patents are patents relating to the thyroid metabolic control loop. The thyroid metabolic control loop describes the brain–pituitary–thyroid axis through hormonal, cellular, and neuro-cognitive analysis.[2] The goal for the control loop is stabilized metabolic regulation, which is critical for human development and survival.[3] Yet, estimates suggest nearly fifty-million Americans have damaged thyroid performance, causing depression, anxiety, and heart disease.[4]

This Article proceeds in two parts. Part I discusses and explains the thyroid gland's hormonal feedback loop, common diseases, available technologies, and treatment options. Part II introduces the Thyroid Patent Dataset, contributing empirical patent analysis to the legal literature. Further, Part II provides legal claims critique and introduces algorithms for calculating damages for patent infringement. In short, this Article explores the thyroid gland's intersection with patent law to advance knowledge in human health, evolve intellectual property, and prompt innovation for biotechnology.

I. Thyroid

The thyroid is a bilobal gland located at the base of the neck in front of the windpipe.[5] The thyroid's functionality, essentially synthesizing thyroid hormone, is meticulously modeled through a feedback loop.[6] The pituitary gland and thyroid communicate instructions for

[2] Larry R. Squire, et al., Fundamental Neuroscience 910 (2008).
[3] Larry R. Squire, et al., Fundamental Neuroscience 909 (2008).
[4] Hypothyroidism, American Thyroid Association, 4 (2013), https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf.
[5] U.S. Patent No. 6,740,680 to Danforth, Jr., et al., Pharmaceutical compositions to tetrac and methods of use thereof (May 25, 2004).
[6] *See* Appendix B. Hypothalamic-Pituitary-Thyroid Axis Model. *See also* C.C. Heuck, et al., Diagnosis and Monitoring of Diseases of The Thyroid, World Health Organization, 8 (2000), https://apps.who.int/iris/handle/10665/66342. *See also* Elske Theresia Massolt, Translational Studies Toward Understanding Clinical Effects of Thyroid Hormone, 9 (2017), https://www.semanticscholar.org/paper/Translational-studies-towards-understanding-effects-Massolt/5631a818b8a4b45b91876c1a4b4af0b2ccf60db6. ("Thyroid hormone is synthesized by the thyroid gland, which is located ventrocaudal of the thyroid cartilage.")

controlling hormone production and stabilization.[7] The system works on an iterative loop where cells in the pituitary gland determine the body's normal hormonal range, known as the set point.[8] In other words, the thyroid produces hormones, which are secreted into the blood and then carried to every tissue in the body.[9] As such, the Thyroid produces a hormonal variety governing the human body's metabolism.[10]

A. Thyroid Hormone

Thyroid hormone synthesis is a three-step process.[11] First, the hypothalamus produces Thyroid Releasing Hormone (TRS),[12] stimulating the pituitary gland[13] to release Thyroid Stimulating Hormone (TSH), Thyrotropin,[14] which in turn activates the thyroid gland. Second, the thyroid gland excretes Thyroxine (T_4) to the bloodstream.[15] Third, T_4 converts to

[7] Hypothyroidism, American Thyroid Association, 10 (2013), https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf.
[8] Hypothyroidism, American Thyroid Association, 10 (2013), https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf.
[9] Hypothyroidism, American Thyroid Association, 4 (2013), https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf.
[10] U.S. Patent No. 6,740,680 to Danforth, Jr., et al., Pharmaceutical compositions to tetrac and methods of use thereof (May 25, 2004).
[11] Elske Theresia Massolt, Translational Studies Toward Understanding Clinical Effects of Thyroid Hormone, 9 (2017), https://www.semanticscholar.org/paper/Translational-studies-towards-understanding-effects-Massolt/5631a818b8a4b45b91876c1a4b4af0b2ccf60db6.
[12] Larry R. Squire, et al., Fundamental Neuroscience 909 (2008). (TRH neurons have long axons that terminate in the median eminence's external zone. This region is highly vascularized by the portal capillary system, which transports TRH to the anterior pituitary gland. There, TRH targets receptors on thyrotropes, which are cells that, when stimulated, produce the thyroid-stimulating hormone. Thyrotropes constitute approximately 10% of the cells in the anterior pituitary gland.)
[13] C.C. Heuck, et al., Diagnosis and Monitoring of Diseases of The Thyroid, World Health Organization, 5 (2000), https://apps.who.int/iris/handle/10665/66342. (Thyroid Stimulating Hormone is a hormone produced by the pituitary gland in response to signals from the hypothalamus.)
[14] Thyrotrope cells in the pituitary gland produce a glycoprotein hormone called thyrotropin, which regulates endocrine function.
[15] C.C. Heuck, et al., Diagnosis and Monitoring of Diseases of The Thyroid, World Health Organization, 8 (2000), https://apps.who.int/iris/handle/10665/66342.

Triiodothyronine (T_3) through deiodination in peripheral tissues.[16] This synthesis is critical for metabolic control in the human body.[17]

As such, Thyroid hormone maintenance is extremely critical for adult metabolic activity, and thyroid hormone abnormalities in adolescence can have catastrophic consequences.[18] Thyroid hormone imbalance can have profound effects on the central nervous system.[19] Interestingly, Thyroid hormone receptors are located throughout the brain, highlighting their importance in central nervous system's development and function.[20] Indeed, T_3 and T_4 also provide feedback to the brain and anterior pituitary gland to regulate TRH and TSH.[21]

i. Thyroxine (T_4)

Thyroxine (T_4) is a hormone the thyroid gland secretes into the bloodstream. Thyroxine plays a crucial role in heart function, metabolism control, brain development, bone health, and muscle control.[22] Distinctly, Thyroxine T_4 contains four iodine atoms per molecule.[23]

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[16] C.C. Heuck, et al., Diagnosis and Monitoring of Diseases of The Thyroid, World Health Organization, 5 (2000), https://apps.who.int/iris/handle/10665/66342. *See also* Kerry Richard, et al., Sulfation of Thyroid Hormone and Dopamine during Human Development: Ontogeny of Phenol Sulfotransferases and Arylsulfatase in Liver, Lung, and Brain, 86 The Journal of Clinical Endocrinology & Metabolism 2734, 2735 (2001).

[17] See Appendix A for Thyroid Control Loop.

[18] Larry R. Squire, et al., Fundamental Neuroscience 909, 910 (2008). (The hypothalamic hormone involved in this function is thyrotropin-releasing hormone, produced by a group of cells in a specific nucleus in the hypothalamus, the paraventricular nucleus.)

[19] Larry R. Squire, et al., Fundamental Neuroscience 912 (2008).

[20] Larry R. Squire, et al., Fundamental Neuroscience 910 (2008). *See also* Elske Theresia Massolt, Translational Studies Toward Understanding Clinical Effects of Thyroid Hormone, 10 (2017), https://www.semanticscholar.org/paper/Translational-studies-towards-understanding-effects-Massolt/5631a818b8a4b45b91876c1a4b4af0b2ccf60db6. (TSH production is stimulated by hypothalamic thyrotropin releasing hormone.)

[21] Id. at 909. *See also* U.S. Patent No. 7,342,127 to Washburn, et al., Substituted anilide ligands for the thyroid receptor (March 11, 2008). (Thyroid hormones are currently used primarily as replacement therapy for patients with hypothyroidism.)

[22] Michelle So, et al., Hypothyroidism: Investigation and management, 41 Australian Family Physician 556, 559 (2020), https://www.racgp.org.au/afp/2012/august/hypothyroidism/.

[23] C.C. Heuck, et al., Diagnosis and Monitoring of Diseases of The Thyroid, World Health Organization, 5 (2000), https://apps.who.int/iris/handle/10665/66342. *See also* Hypothyroidism, American Thyroid Association, 4 (2013), https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf. (The main hormone made by the thyroid is thyroxine, also called T_4 because it contains four iodine molecules.)

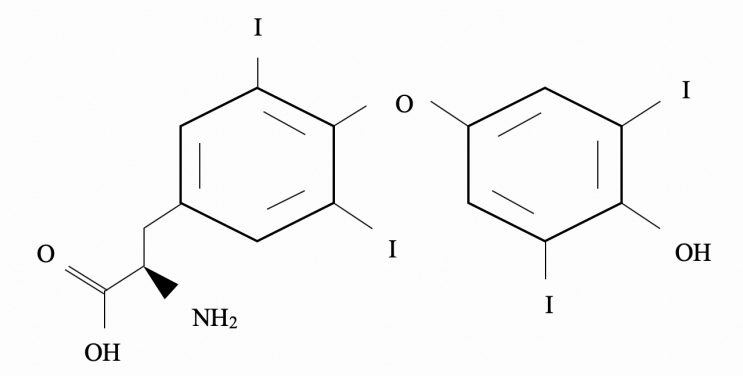

Figure 1[24]

As blood flows through the pituitary gland, cells measure T_4 levels to determine set point accuracy.[25] The pituitary cells communicate with the thyroid through TSH secretion.[26]

When T_4 levels are at a set point,[27] the pituitary gland sends out enough TSH to tell the thyroid to maintain homeostasis.[28] If the T_4 levels get low, the pituitary gland releases more TSH, telling the thyroid to make more T_4.[29] Conversely if T_4 are high, the pituitary gland releases less TSH to slow production.[30] For some patients, Thyroxine replacement may be beneficial where TSH levels are elevated however, this remains controversial.[31] Indeed, T_3 has greater biological activity than T_4 comparatively.[32]

[24] Thyroxine Molecule.
[25] Hypothyroidism, American Thyroid Association, 10 (2013), https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf.
[26] Hypothyroidism, American Thyroid Association, 10 (2013), https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf.
[27] A set point is a predetermined hormone level.
[28] Hypothyroidism, American Thyroid Association, 10 (2013), https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf.
[29] Hypothyroidism, American Thyroid Association, 10 (2013), https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf.
[30] Michelle So, et al., Hypothyroidism: Investigation and management, 41 Australian Family Physician 556, 556 (2020), https://www.racgp.org.au/afp/2012/august/hypothyroidism/. ("The significance of elevated TSH associated with thyroid hormones within normal range is controversial; thyroxine replacement may be beneficial in some cases.")
[31] Michelle So, et al., Hypothyroidism: Investigation and management, 41 Australian Family Physician 556, 561 (2020), https://www.racgp.org.au/afp/2012/august/hypothyroidism/.
[32] Larry R. Squire, et al., Fundamental Neuroscience 911 (2008).

ii. Triiodothyronine (T_3)

T_4 converts to the active Triiodothyronine (T_3) within cells and peripheral tissues by deiodinases.[33] As such, in contrast to T_4, the T_3 molecule contains three iodine atoms.[34]

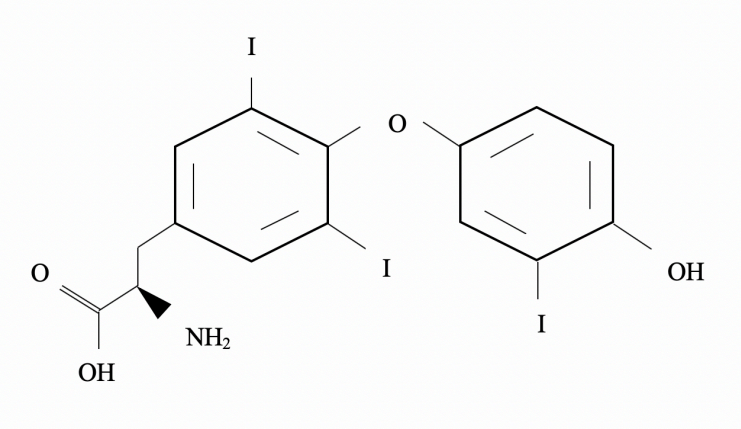

Figure 2[35]

T_3 is the physiologically active thyroid hormone.[36] It controls myocardium properties, heart rate, and vascular function.[37] In fact, T_3 affects almost every process in the body.[38]

Interestingly, one report suggests the thyroid gland produces T_3 directly.[39] Although, thyroid disease is typically not treated with T_3 supplementation. However, some researchers speculate a T_4 and T_3 combination might be better.[40] Molecular structures are important because

[33] C.C. Heuck, et al., Diagnosis and Monitoring of Diseases of The Thyroid, World Health Organization, 5 (2000), https://apps.who.int/iris/handle/10665/66342. (Once in the bloodstream, thyroxine travels to the body's organs, where it is converted to an active form, triiodothyronine T_3.)
[34] C.C. Heuck, et al., Diagnosis and Monitoring of Diseases of The Thyroid, World Health Organization, 5 (2000), https://apps.who.int/iris/handle/10665/66342.
[35] Triiodothyronine Molecule.
[36] Rastogi, M.V., LaFranchi, S.H. Congenital hypothyroidism, 5 Orphanet J. Rare Disease, 12-13 (2010), https://doi.org/10.1186/1750-1172-5-17. (Although T_3 is the biologically active form of the hormone, most T_3 in the brain is formed from local deiodination of T_4; thus, T_3 replacement is not needed for normal neurologic functioning.)
[37] Elske Theresia Massolt, Translational Studies Toward Understanding Clinical Effects of Thyroid Hormone, 33 (2017), https://www.semanticscholar.org/paper/Translational-studies-towards-understanding-effects-Massolt/5631a818b8a4b45b91876c1a4b4af0b2ccf60db6.
[38] C.C. Heuck, et al., Diagnosis and Monitoring of Diseases of The Thyroid, World Health Organization, 5 (2000), https://apps.who.int/iris/handle/10665/66342.
[39] Institute for Quality and Efficiency in Health Care (IQWiG), How does the thyroid gland work?, (November 17, 2010), https://www.ncbi.nlm.nih.gov/books/NBK279388/. (They are made in what are known as the follicular epithelial cells of the thyroid.)
[40] Hypothyroidism, American Thyroid Association, 17 (2013), https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf.

clinical effects resulting from thyroid hormone imbalance are observable at the cellular level.[41] Thyroid diseases are influenced by endocrine physiology, particularly where abnormal thyroid hormone concentrations affect organ function resulting in clinical symptoms.[42]

B. Thyroid Disease

Second only to diabetes, thyroid diseases are the most ubiquitous endocrine disorders worldwide.[43] Although thyroid diseases may be life threatening, they are often curable.[44] Abnormal biochemical thyroid function reports substantiate substantial populations suffer from subclinical conditions.[45] Subclinical conditions have subtle manifestations and may mimic other diseases.[46] And, among patients taking thyroid medication, only 60% were within the normal range of TSH.[47] In short, modest TSH fluctuations corresponded to physiological changes affecting patient health.[48]

Thyroid dysfunction is common, often undetected, and may be associated with adverse health outcomes.[49] Identifying thyroid disease is challenging because symptoms often develop so

[41] Elske Theresia Massolt, Translational Studies Toward Understanding Clinical Effects of Thyroid Hormone, 9 (2017), https://www.semanticscholar.org/paper/Translational-studies-towards-understanding-effects-Massolt/5631a818b8a4b45b91876c1a4b4af0b2ccf60db6.
[42] Elske Theresia Massolt, Translational Studies Toward Understanding Clinical Effects of Thyroid Hormone, 9 (2017), https://www.semanticscholar.org/paper/Translational-studies-towards-understanding-effects-Massolt/5631a818b8a4b45b91876c1a4b4af0b2ccf60db6.
[43] C.C. Heuck, et al., Diagnosis and Monitoring of Diseases of The Thyroid, World Health Organization, 8 (2000), https://apps.who.int/iris/handle/10665/66342.
[44] C.C. Heuck, et al., Diagnosis and Monitoring of Diseases of The Thyroid, World Health Organization, 9 (2000), https://apps.who.int/iris/handle/10665/66342.
[45] Gay J. Canaris, MD, et al., The Colorado Thyroid Disease Prevalence Study 160 Arch Intern Med. 526, 526 (2000), doi:10.1001/archinte.160.4.526.
[46] C.C. Heuck, et al., Diagnosis and Monitoring of Diseases of The Thyroid, World Health Organization, 9 (2000), https://apps.who.int/iris/handle/10665/66342.
[47] Gay J. Canaris, MD, et al., The Colorado Thyroid Disease Prevalence Study 160 Arch Intern Med. 526, 526 (2000), doi:10.1001/archinte.160.4.526.
[48] Gay J. Canaris, MD, et al., The Colorado Thyroid Disease Prevalence Study 160 Arch Intern Med. 526, 526 (2000), doi:10.1001/archinte.160.4.526.
[49] Gay J. Canaris, MD, et al., The Colorado Thyroid Disease Prevalence Study 160 Arch Intern Med. 526, 526 (2000), doi:10.1001/archinte.160.4.526.

subtly that they go unnoticed.[50] The difficulty with many studies lies in the variable disease state definitions, where poorly defined populations are studied with limited thyroid functional measures.[51] Additionally, studies from various countries differ in their estimates for both hypothyroidism and hyperthyroidism.[52]

i. Hypothyroidism

An estimated 2% – 3% of Americans have clinical hypothyroidism and 10% – 15% have sub-clinical hypothyroidism.[53] In other words, roughly 6,600,000 – 9,900,000 Americans have severe hypothyroidism; while 33,000,000 – 49,500,000 Americans have mild hypothyroidism. Further, more than half of people with hypothyroidism do not know they have it.[54] And, approximately 10% – 15% of patients with hypothyroidism display significant psychological impairment.[55] Additionally, hypothyroidism is more common in biological females than biological males, and more common in the elderly than young.[56]

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[50] Gay J. Canaris, MD, et al., The Colorado Thyroid Disease Prevalence Study 160 Arch Intern Med. 526, 527 (2000), doi:10.1001/archinte.160.4.526.

[51] Gay J. Canaris, MD, et al., The Colorado Thyroid Disease Prevalence Study 160 Arch Intern Med. 526, 526 (2000), doi:10.1001/archinte.160.4.526. *See also* Elske Theresia Massolt, Translational Studies Toward Understanding Clinical Effects of Thyroid Hormone, 49 (2017), https://www.semanticscholar.org/paper/Translational-studies-towards-understanding-effects-Massolt/5631a818b8a4b45b91876c1a4b4af0b2ccf60db6. ("Thyroid peroxidase is the major autoantigen and TPO antibodies are present in almost all patients with autoimmune hypothyroidism and precede the clinical phase of autoimmune hypothyroidism by many years.")

[52] Gay J. Canaris, MD, et al., The Colorado Thyroid Disease Prevalence Study 160 Arch Intern Med. 526, 526 (2000), doi:10.1001/archinte.160.4.526.

[53] Hypothyroidism, American Thyroid Association, 4 (2013), https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf.

[54] Hypothyroidism, American Thyroid Association, 4 (2013), https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf.

[55] Elske Theresia Massolt, Translational Studies Toward Understanding Clinical Effects of Thyroid Hormone, 9 (2017), https://www.semanticscholar.org/paper/Translational-studies-towards-understanding-effects-Massolt/5631a818b8a4b45b91876c1a4b4af0b2ccf60db6.

[56] Michelle So, et al., Hypothyroidism: Investigation and management, 41 Australian Family Physician 556, 556 (2020), https://www.racgp.org.au/afp/2012/august/hypothyroidism/. ("Unless contraindicated, iodine supplementation should be prescribed routinely in women planning a pregnancy.")

There several types of hypothyroidism. For example, Congenital Hypothyroidism (CH) is defined as thyroid hormone deficiency present at birth.[57] CH describes an organism with insufficient thyroid hormone during early neonatal development.[58] Thyroid hormone deficiency at birth is most commonly caused by a problem with the gland's physical development or impaired thyroid hormone biosynthesis.[59]

A second example is autoimmune hypothyroidism, which is characterized by a clinical feature combination including, elevated serum TSH with reduced Free T_4 levels, serum antibodies against thyroid antigens, and reduced echogenicity in the thyroid sonogram.[60] In fact, thyroid autoimmunity is the most common causes of hypothyroidism, Hashimoto's disease.[61] Hypothyroidism, has several causes.[62] For example, the thyroid must have iodine to make thyroid hormone.[63] Too much iodine may also cause and worsen hypothyroidism.[64] In the Western World, hypothyroidism is most commonly caused by autoimmune chronic lymphocytic

[57] Rastogi, M.V., LaFranchi, S.H. Congenital hypothyroidism, 5 Orphanet J. Rare Disease, 1 (2010), https://doi.org/10.1186/1750-1172-5-17.
[58] Larry R. Squire, et al., Fundamental Neuroscience 912 (2008).
[59] Rastogi, M.V., LaFranchi, S.H. Congenital hypothyroidism, 5 Orphanet J. Rare Disease, 1 (2010), https://doi.org/10.1186/1750-1172-5-17. ("In iodine sufficient countries, 85% of congenital hypothyroidism is due to thyroid dysgenesis.")
[60] Elske Theresia Massolt, Translational Studies Toward Understanding Clinical Effects of Thyroid Hormone, 49 (2017), https://www.semanticscholar.org/paper/Translational-studies-towards-understanding-effects-Massolt/5631a818b8a4b45b91876c1a4b4af0b2ccf60db6.
[61] Elske Theresia Massolt, Translational Studies Toward Understanding Clinical Effects of Thyroid Hormone, 12 (2017), https://www.semanticscholar.org/paper/Translational-studies-towards-understanding-effects-Massolt/5631a818b8a4b45b91876c1a4b4af0b2ccf60db6. ("It is the most common organ-specific autoimmune disorder with an estimated prevalence of 2%, with a higher prevalence in women and depending on iodine intake.")
[62] U.S. Patent No. 6,740,680 to Danforth, Jr., et al., Pharmaceutical compositions to tetrac and methods of use thereof (May 25, 2004).
[63] Hypothyroidism, American Thyroid Association, 8 (2013), https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf.
[64] Hypothyroidism, American Thyroid Association, 8 (2013), https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf.

thyroiditis.[65] However, worldwide, iodine deficiency is the most common cause for hypothyroidism, although it is a rare cause in the U.S.[66]

Hypothyroid symptoms include anxiety, weakness, heart disease, constipation, depression, and weight gain.[67] Further, many patients report ongoing symptoms such as muscle aching and tiredness.[68] Hypothyroidism cannot be cured but it can be treated and controlled.[69] In fact, most disease related deficiencies can be mitigated by newborn infant screening and thyroid hormone replacement.[70]

ii. Hyperthyroidism

Hyperthyroidism describes an excess thyroid hormone causing the pituitary gland to produce less TSH.[71] TSH measurement is the base for the hyperthyroidism diagnosis.[72] In short, low TSH and high T_3 and T_4 corresponds to hyperthyroidism.[73] Thyroid gland overactivity has several causes.[74] Hyperthyroidism symptoms include sweating, heart palpitations, and weight

[65] Michelle So, et al., Hypothyroidism: Investigation and management, 41 Australian Family Physician 556, 556 (2020), https://www.racgp.org.au/afp/2012/august/hypothyroidism/. ("A thyroid peroxidase antibody assay is the only test required to confirm the diagnosis of autoimmune thyroiditis.")
[66] Hypothyroidism, American Thyroid Association, 8 (2013), https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf.
[67] Elske Theresia Massolt, Translational Studies Toward Understanding Clinical Effects of Thyroid Hormone, 123 (2017), https://www.semanticscholar.org/paper/Translational-studies-towards-understanding-effects-Massolt/5631a818b8a4b45b91876c1a4b4af0b2ccf60db6.
[68] Elske Theresia Massolt, Translational Studies Toward Understanding Clinical Effects of Thyroid Hormone, 9 (2017), https://www.semanticscholar.org/paper/Translational-studies-towards-understanding-effects-Massolt/5631a818b8a4b45b91876c1a4b4af0b2ccf60db6.
[69] Hypothyroidism, American Thyroid Association, 12 (2013), https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf.
[70] Michelle So, et al., Hypothyroidism: Investigation and management, 41 Australian Family Physician 556, 556 (2020), https://www.racgp.org.au/afp/2012/august/hypothyroidism/. ("The initial screening for suspected hypothyroidism is thyroid stimulating hormone.")
[71] C.C. Heuck, et al., Diagnosis and Monitoring of Diseases of The Thyroid, World Health Organization, 5 (2000), https://apps.who.int/iris/handle/10665/66342.
[72] C.C. Heuck, et al., Diagnosis and Monitoring of Diseases of The Thyroid, World Health Organization, 5 (2000), https://apps.who.int/iris/handle/10665/66342.
[73] U.S. Patent No. 6,740,680 to Danforth, Jr., et al., Pharmaceutical compositions to tetrac and methods of use thereof (May 25, 2004).
[74] U.S. Patent No. 6,740,680 to Danforth, Jr., et al., Pharmaceutical compositions to tetrac and methods of use thereof (May 25, 2004).

loss.[75] Additional symptoms include increased body temperature, decreased body weight, decreased serum cholesterol, increased stroke volume, and arrhythmia.[76] Excessive thyroid hormone, can also result in symptoms such as tremor, nervousness, insomnia, and impairments in memory and concentration.[77]

Hyperthyroidism is characterized by excessive secretion of thyroid hormones; the most common cause is the autoimmune disorder Graves' disease.[78] Graves' hyperthyroidism is a hypermetabolic state, affecting virtually every tissue and cell in the body and leads to cardiovascular dysfunction and death.[79] Graves' hyperthyroidism is treated by surgical resection,[80] therapeutic doses of radioactive iodine, or pharmacologically.[81] However, each of these treatment modalities has side effects associated with it.[82] Often, both Hypothyroidism and Hyperthyroidism are treatable with lifelong synthetic thyroid hormone replacement.[83]

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[75] Elske Theresia Massolt, Translational Studies Toward Understanding Clinical Effects of Thyroid Hormone, 9 (2017), https://www.semanticscholar.org/paper/Translational-studies-towards-understanding-effects-Massolt/5631a818b8a4b45b91876c1a4b4af0b2ccf60db6.

[76] U.S. Patent No. 7,230,031 to Shiohara, et al., Thyroid hormone receptor ligand, medicinal compositions containing the same and use thereof (June 12, 2007). (Assigned to Kissei Pharmaceutical Co., Ltd.)

[77] Larry R. Squire, et al., Fundamental Neuroscience 912 (2008).

[78] U.S. 9,206,154, to Gershengorn, et al., Inverse agonists and neutral antagonists for the TSH receptor (December 8, 2015).

[79] U.S. 9,206,154, to Gershengorn, et al., Inverse agonists and neutral antagonists for the TSH receptor (December 8, 2015). (Graves' hyperthyroid patients as diagnosed by computerized tomographic scan.)

[80] Hypothyroidism, American Thyroid Association, 7 (2013), https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf. ("Some people with thyroid nodules, thyroid cancer, or Graves' disease need to have part or the entire thyroid removed.")

[81] U.S. 9,206,154, to Gershengorn, et al., Inverse agonists and neutral antagonists for the TSH receptor (December 8, 2015).

[82] U.S. 9,206,154, to Gershengorn, et al., Inverse agonists and neutral antagonists for the TSH receptor (December 8, 2015).

[83] U.S. Patent No. 6,740,680 to Danforth, Jr., et al., Pharmaceutical compositions to tetrac and methods of use thereof (May 25, 2004).

C. Treatment

The treatment options available for thyroid disease depend heavily on the nature and extent to which the body produces and regulates thyroid hormone levels.[84] For example, Hypothyroidism is usually treated by replacing the hormone the Thyroid fails to produce with synthetic hormone.[85] By contrast, Hyperthyroidism may be treated by surgically destroying part of the thyroid gland.[86] In all cases, proper treatment for thyroid disease is vital to patient health.[87] Thyroid hormone imbalance can have deleterious and disastrous consequences including extreme anxiety, depression, and fatigue.[88]

i. Medication

Medication options for treating thyroid disease range depending on the clinical diagnosis and individual patient response. For hypothyroidism, physicians often prescribe synthetic thyroxine.[89] Synthetic thyroxine pills contain hormone like the T_4, which a healthy thyroid makes naturally.[90] In other words, synthetic thyroxine replaces the hormone that the thyroid can

[84] U.S. Patent No. 6,555,581 to Franz, et al., Levothyroxine compositions and methods (April 29, 2003). ("Thyroid hormone replacement therapy is a chronic and lifetime endeavor for treatment. Thyroid hormone dosage must be established for each patient individually.")
[85] Hypothyroidism, American Thyroid Association, 12 (2013), https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf. *See also* Larry R. Squire, et al., Fundamental Neuroscience 912 (2008). ("For example, Hypothyroidism generally is treated by thyroid hormone replacement.")
[86] U.S. Patent No. 6,740,680 to Danforth, Jr., et al., Pharmaceutical compositions to tetrac and methods of use thereof (May 25, 2004).
[87] U.S. Patent No. 7,342,127 to Washburn, et al., Substituted anilide ligands for the thyroid receptor (March 11, 2008). ("In hyperthyroidism, these hormones lead to weight loss, hypermetabolism, lowering of serum LDL levels, cardiac arrhythmias, heart failure, muscle weakness, bone loss in postmenopausal women, and anxiety.")
[88] U.S. Patent No. 6,555,581 to Franz, et al., Levothyroxine compositions and methods (April 29, 2003). *See also* Hypothyroidism, American Thyroid Association, 18 (2013), https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf. ("The most common symptoms of too much thyroid hormone are fatigue, the inability to sleep, greater appetite, nervousness, shakiness, feeling hot when other people are cold, muscle weakness, shortness of breath, and a racing, skipping heart.")
[89] U.S. Patent No. 6,936,274 to Hanshew, Jr., et al., Storage stable thyroxine active drug formulations and methods for their production (August 30, 2005).
[90] Hypothyroidism, American Thyroid Association, 12 (2013), https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf.

no longer make.[91] Oral levothyroxine (LT_4) is the standard therapy for patients with hypothyroidism.[92] Both brand-name and generic LT_4 tablets are available.[93]

Variations in hyperthyroidism manifestations and corresponding cardiovascular concerns limit treatment options for hypothyroid symptoms.[94] However, drug therapy for hyperthyroidism typically involves antithyroid drugs.[95] Two main antithyroid drugs are propylthiouracil and methimazole, which inhibit organic iodine binding.[96] Additionally, in some cases treatment with glucocorticoids[97] has shown limited effect in treating hyperthyroidism.[98]

Yet, key problems persist. For example, pharmacists often switch between LT_4 formulations which have been determined bioequivalent.[99] However, even small differences

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[91] Hypothyroidism, American Thyroid Association, 13 (2013), https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf.

[92] There are three major problems with daily oral levothyroxine for treating hypothyroidism: (1) Fluctuation in ingestion times and surrounding dietary conditions causes metabolic imbalance, (2) Fluctuation in patient needs causes metabolic imbalance, and (3) Fluctuation in brand name may cause metabolic imbalance. The disclosed invention solves these three problems, providing methods for curing hypothyroidism with automatic monitoring and corrective release to maintain metabolic homeostasis. *See* Nienke Bolk, MD, et al., Effects of Evening vs Morning Levothyroxine Intake, 1 (2010), doi:10.1001/archinternmed.2010.436.

[93] *See* Appendix D. *See also* Hypothyroidism, American Thyroid Association, 17 (2013), https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf. (In the United States, thyroxine pills contain only T4. However, some researchers speculate whether a combination of T4 and T3 might be better for treating patients. While there have been some early studies, the results have not been particularly promising.)

[94] U.S. Patent No. 7,342,127 to Washburn, et al., Substituted anilide ligands for the thyroid receptor (March 11, 2008). ("Prior attempts to utilize thyroid hormones pharmacologically to treat these disorders have been limited by manifestations of hyperthyroidism, and in particular by cardiovascular toxicity.)

[95] U.S. Patent No. 6,740,321 to Donovan, Method for treating thyroid disorders with a botulinum toxin (May 25, 2004). (Assigned to Allergan, Inc.)

[96] U.S. Patent No. 6,740,321 to Donovan, Method for treating thyroid disorders with a botulinum toxin (May 25, 2004). (Assigned to Allergan, Inc.)

[97] Glucocorticoids are corticosteroids, a class of steroid hormones. Glucocorticoids bind to the glucocorticoid receptor in cells.

[98] U.S. 9,206,154, to Gershengorn, et al., Inverse agonists and neutral antagonists for the TSH receptor (December 8, 2015).

[99] Salvatore Benvenga, Allan Carle´, Levothyroxine Formulations: Pharmacological and Clinical Implications of Generic Substitution, 36 Advances in Therapy 59, 59 (2019), https://doi.org/10.1007/s12325-019-01079-1. ("In the US, the Food and Drug Administration (FDA) has developed a protocol for establishing bioequivalence of LT4 formulations based on serum thyroxine (T4) levels after a single oral dose administered to healthy volunteers.") *See also* Hypothyroidism, American Thyroid Association, 15 (2013), https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf. ("This is because generic drugs can be substituted with other generic drugs from different manufacturers of levothyroxine each time you get your prescriptions refilled.")

between LT_4 formulations can cause significant changes in TSH levels.[100] Changes may cause clinical symptoms, some of which can be caused by inactive ingredients.[101] As such, pharmaceutical swapping is a particular concern in vulnerable populations, including elderly, pregnant, and pediatric patients.[102]

ii. Technologies

Technology is a new and better way to function. In developing new technologies, it is generally advisable to start by defining a problem. However, economics and politics are often the driving force in scaling technical development for biotechnology.[103] Although, simple exploration has proven effective in certain domains.

For example, exploring the thyroid in new ways may radically improve diagnostics for thyroid disease.[104] Indeed, imaging technologies like ultrasound[105] and MRI,[106] are improving

[100] Salvatore Benvenga, Allan Carle´, Levothyroxine Formulations: Pharmacological and Clinical Implications of Generic Substitution, 36 Advances in Therapy 59, 59 (2019), https://doi.org/10.1007/s12325-019-01079-1.
[101] See Appendix D. *See also* Salvatore Benvenga, Allan Carle´, Levothyroxine Formulations: Pharmacological and Clinical Implications of Generic Substitution, 36 Advances in Therapy 59, 59 (2019), https://doi.org/10.1007/s12325-019-01079-1. (Patients should be maintained on the same LT_4 preparation if possible. If the LT_4 preparation is changed, TSH levels should be evaluated and, if necessary, the dose of LT_4 adjusted.)
[102] Salvatore Benvenga, Allan Carle´, Levothyroxine Formulations: Pharmacological and Clinical Implications of Generic Substitution, 36 Advances in Therapy 59, 59 (2019), https://doi.org/10.1007/s12325-019-01079-1.
[103] Brian S. Haney, Automated Source Selection Scoring & FAR Compliance, 48 Pub. Cont. L.J. 751, 752 (2019), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3261360. (Discussing the federal budget in the context of public procurement and technology acquisition.)
[104] Endocrine Society, Thyroid, Endocrine Facts and Figures, 6 (2015), https://www.endocrine.org/-/media/endocrine/files/facts-and-figures/endocrine_facts_figures_thyroidpw.pdf. (A second example for exploration-based developments in thyroid technologies is fine need aspiration biopsy. In fact, from 2006 to 2011, FNA use more than doubled, with a 16% annual growth. Recent reports credit FNA biopsies with an increase in the diagnostic yield of cancers at thyroidectomy. Interestingly, while indeterminate cytology can be found in 15-30% of FNA specimens, other studies report ultrasound guided FNA procedures yield lower rates of both non-diagnostic and false-negative cytology specimens.)
[105] Rastogi, M.V., LaFranchi, S.H. Congenital hypothyroidism, 5 Orphanet J. Rare Disease, 12 (2010), https://doi.org/10.1186/1750-1172-5-17. ("Thyroid ultrasonography is accurate in confirming true thyroid aplasia, or thyroid failure.")
[106] Taewoo Kang, et al., Magnetic Resonance Imaging Features of Normal Thyroid Parenchyma and Incidental Diffuse Thyroid Disease: A Single-Center Study, Frontiers in Endocrinology, 1, 1 (2018), doi: 10.3389/fendo.2018.00746. (Concluding MRI may be helpful for thyroid disease detection.) *See also* Simone Schuerle, et al., Genetic Encoding of Targeted Magnetic Resonance Imaging Contrast Agents for Tumor Imaging F (2020), https://dx.doi.org/10.1021/acssynbio.9b00416.

thyroid disease diagnostics.[107] Studies report thyroid nodules are up to ten times as likely to be detected with ultrasound compared to physical examination alone.[108] Yet, thyroid ultrasonography is usually only investigated with concern regarding structural thyroid abnormalities.[109] And still, functional abnormalities cause significant symptoms.[110]

Creating technology by defining problems to solve is not necessarily an easy or fluent task because syntactic variations for problems are vast. For example, one way to phrase a problem is there is no cure for hypothyroidism.[111] Alternatively, the problem may be reformulated, the thyroid gland does not produce enough T_4. Another way, the patient's blood results show low T_4 levels. Or, the Hypothalamic-Pituitary-Thyroid Axis is operating at sub-optimal levels for maintaining proper metabolic control.

For some, writing and defining the problem is the most difficult task in technical development. For others, the problem is just the beginning. Inventions are technical solutions to problems. However, inventors wishing to bring their inventions to life through scalable production and commercialization face significant regulatory barriers protecting market

[107] Endocrine Society, Thyroid, Endocrine Facts and Figures, 6 (2015), https://www.endocrine.org/-/media/endocrine/files/facts-and-figures/endocrine_facts_figures_thyroidpw.pdf. See also Rastogi, M.V., LaFranchi, S.H. Congenital hypothyroidism, 5 Orphanet J. Rare Disease, 12 (2010), https://doi.org/10.1186/1750-1172-5-17. ("In the situations described above where radionuclide uptake and scan show absent uptake, but a gland is actually present, ultrasonography may show a thyroid gland in a specific location.")

[108]Endocrine Society, Thyroid, Endocrine Facts and Figures, 6 (2015), https://www.endocrine.org/-/media/endocrine/files/facts-and-figures/endocrine_facts_figures_thyroidpw.pdf. ("Use of imaging technologies, such as ultrasound, CT, and magnetic resonance imaging (MRI), has led to more thyroid nodule diagnosis than in the past, when physical examination was the primary mode of diagnosis.")

[109] Michelle So, et al., Hypothyroidism: Investigation and management, 41 Australian Family Physician 556, 556 (2020), https://www.racgp.org.au/afp/2012/august/hypothyroidism/.

[110] U.S. Patent No. 7,230,031 to Shiohara, et al., Thyroid hormone receptor ligand, medicinal compositions containing the same and use thereof (June 12, 2007). ("In patients with hypothyroidism, decreased body temperature, increased body weight, increased serum cholesterol, decreased cardiac functions, liver function disorders, depression, dry skins or alopecia are observed.")

[111] Hypothyroidism, American Thyroid Association, 22 (2013), https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf.

incumbents.[112] For example, the patent system is fine-tuned and tailored to favor large corporations and exclude inventors.[113]

II. Patents

From an informatics perspective, a patent is a document containing invention data.[114] In this view, patents are made up with information bytes, binary logic compressed to macro-scales. From an economic perspective a patent is a gamble.[115] According to the Economist, "Patents are like lotteries, in which there are a few prizes and a great many blanks."[116] Legally, a patent is a monopoly.[117] A legal protection for new technologies,[118] the patent provides the holder the right to prohibit others from using, making, or selling an invention.[119]

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[112] Brian S. Haney, Quantum Patents, 27 B.U. J. Sci. & Tech. L. __ (2020)(Forthcoming), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3554925. (Discussing standards for patentability and post-prosecution litigation.)

[113] USPTO, USPTO Fee Schedule (2020), https://www.uspto.gov/learning-and-resources/fees-and-payment/uspto-fee-schedule. *See also* Public Law 112-29, Leahy-Smith America Invents Act (September 16, 2011). (See Section 11 fees for patent services, which de facto prevents inventors living in poverty from being able to patent or protect their inventions.)

[114] Michael Buckland, Information and Society 21-23 (2017). (Discussing document definitions.)

[115] Edward O. Thorpe, Blackjack Systems (1975), http://www.edwardothorp.com/wp-content/uploads/2016/11/BlackjackSystems.pdf.

[116] The Economist: Volume 9, Part 2, 811 (January 1, 1851), https://books.google.com/books?id=k0lUAAAAcAAJ&pg=PA811&lpg=PA811&dq=the+economist+Patents+are+like+lotteries,+in+which+there+are+a+few+prizes+and+a+great+many+blanks.&source=bl&ots=sCsCAN0AEz&sig=ACfU3U37GG1N9m2gEyZX2jkVObYrJRXwGA&hl=en&sa=X&ved=2ahUKEwiPvuja8t7pAhWGoXIEHTSHCvsQ6AEwAnoECAcQAQ#v=onepage&q=the%20economist%20Patents%20are%20like%20lotteries%2C%20in%20which%20there%20are%20a%20few%20prizes%20and%20a%20great%20many%20blanks.&f=false.

[117] Stephen Yelderman, *The Value of Accuracy in The Patent System*, 84 U. CHI. L. REV. 1217, 1270 (2017). *See* U.S. Const. art. I, § 8, cl. 8. (Providing the constitutional basis for patents, "The Congress shall have the Power…To promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries.") *See also* Andrew Beckerman-Rodau, The Problem with Intellectual Property Rights: Subject Matter Expansion, 13 Yale J. L. & Tech. 36, 55 (2010-2011).(The USPTO's granting of patent rights provides typical property rights, including the right of the patent owner to exclude others from making, using, offering for sale, or selling the invention throughout the United States or importing the invention into the United States.)

[118] JOHN PALFREY, INTELLECTUAL PROPERTY STRATEGY 55 (MIT Press 2012).

[119] Stephen Yelderman, *The Value of Accuracy in The Patent System*, 84 U. CHI. L. REV. 1217, 1270 (2017), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2925216. *See also* U.S. Const. art. I, § 8, cl. 8. (Providing the constitutional basis for patents, "The Congress shall have the Power…To promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries.")

A. Legal Claims

Claims are the most important part of a patent[120] because claims are the only part of the patent that can be infringed.[121] The USPTO issues patents for claims it determines satisfy the statutory requirements.[122] Further, a challenge to an issued patent will succeed if the challenger can show that any of the requirements have not been met.[123] Further, courts construe patent claims by starting with the plain meaning, as the terms are understood by a person having ordinary skill in the art.[124] Three claim drafting considerations crucial to Thyroid Patents are: nonobviousness, novelty, and scope.

i. Nonobviousness

The nonobviousness doctrine seeks to ensure patents are granted only for technologically significant advances to stimulate useful innovation.[125] A patent claim is invalid "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious ... to a person having ordinary skill in the art".[126] NYU Law Professor Jeanne Fromer explains, "The nonobviousness doctrine seeks to ensure that patents are granted only for technologically significant advances to foster the patent system's goal of stimulating useful innovation." [127]

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[120] Mark A. Lemley, *The Changing Meaning of Patent Claim Terms,* 104 MICH. L. REV. 101, 101 (2005).
[121] Kevin F. O'Malley, et. al., 3A FED. JURY PRAC. & INSTR. § 158:41 (6th ed. 2019).
[122] Max Stul Oppenheimer, Patents 101: Patentable Subject Matter and Separation of Powers, 15 VAND. J. ENT. & TECH. L. 1, 4 (2012).
[123] Max Stul Oppenheimer, Patents 101: Patentable Subject Matter and Separation of Powers, 15 VAND. J. ENT. & TECH. L. 1, 4 (2012).
[124] Mark A. Lemley, The Changing Meaning of Patent Claim Terms, 104 Mich. L. Rev. 101, 102 (2005).
[125] Jeanne C. Fromer, The Layers of Obviousness in Patent Law, 22 HARV. J. OF L. & TECH., 75 (2008). https://papers.ssrn.com/sol3/papers.cfm?abstract_id=1119723. ("The nonobviousness doctrine seeks to ensure that patents are granted only for technologically significant advances to foster the patent system's goal of stimulating useful innovation.")
[126]35 U.S.C. § 103 (2013).
[127] Jeanne C. Fromer, The Layers of Obviousness in Patent Law, 22 HARV. J. OF L. & TECH., 75 (2008). https://papers.ssrn.com/sol3/papers.cfm?abstract_id=1119723.

The statute requires that obviousness be judged from the perspective of the person having ordinary skill in the art.[128] Consider U.S. Patent No. 6,740,680, *Pharmaceutical compositions to tetrac and methods of use thereof*, which claims:

> "1. A method for suppressing TSH secretion while reducing or avoiding the thyromimetic stimulation of peripheral tissues induced by a dose of L-thyroxine which produces an equivalent TSH-suppressive effect comprising administration of a pharmaceutical composition comprising tetrac, or a pharmaceutically acceptable salt thereof, admixed with a pharmaceutically acceptable carrier."[129]

Here, the nonobvious advance composed two elements, suppressing TSH secretion and a pharmaceutical composition including Tetrac[130] and other compounds. Until this patent, the state-of-the-art reflects Levothyroxine[131] was considered the only pharmaceutical composition capable of treating thyroid disease.

Nonobviousness is a question of law,[132] but it relies upon factual inquiries surrounding the differences between the prior art and the application's claims.[133] The goal for the nonobviousness requirement is to limit patents to only those inventions representing a sufficiently large advance over previously known technology.[134] To one skilled-in-the-art, the

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[128]Endress + Hauser Inc. v. Hawk Meas. Sys. Pty., 122 F.3d 1040, 1042 (Fed. Cir. 1997). (Analogizing the person having ordinary skill in the art to the reasonable man in criminal law.) *See also* Dean Alderucci, *The Automation of Legal Reasoning: Customized AI Techniques for the Patent Field*, 58 Duq. L.R. 50 (2020).

[129] U.S. Patent No. 6,740,680 to Danforth, Jr., et al., Pharmaceutical compositions to tetrac and methods of use thereof (May 25, 2004).

[130] Maria E. Everts, et al., *Uptake of 3,3',5,5'-tetraiodothyroacetic acid and 3,3',5'-triiodothyronine in cultured rat anterior pituitary cells and their effects on thyrotropin secretion*, 136 Endocrinology 4454 (1995), DOI: 10.1210/en.136.10.4454.

[131] U.S. Patent No. 6,555,581 to Franz, et al., Levothyroxine compositions and methods (April 29, 2003).

[132]Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966).

[133] Brian S. Haney, *Patents for NLP Software: An Empirical Review*, 22 N.C. J.L. & Tech. __ (2020), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3594515. (One idea is to measure these factual considerations objectively to identify probabilistic correlation. For example, the relationship between the prior art and the patent could be objectively measured according to the relative syntactic similarity between the prior art claims and patent claims.)

[134] *Sensonics, Inc. v. Aerosonic Corp*., 81 F.3d 1566, 1570 (Fed. Cir. 1996).

degree to which an invention advances the art may be entirely subjective.[135] And yet, in addition to nonobvious, patentable claims must also be for something new.

ii. Novelty

A second component for patent claims is that they must claim a novel invention.[136] In fact, patents are validated technical advancements for new products and innovation services.[137] The law requires that an invention be novel, or new, to be granted a patent.[138] Consider U.S. Patent. No. 7,493,172, *Methods and systems for stimulating a nerve originating in an upper cervical spine area to treat a medical condition*, which claims:

> "1. A method of treating a medical condition of a patient, said method comprising: applying at least one stimulus to a target nerve within a patient with an implanted system control unit in accordance with one or more stimulation parameters configured to treat said medical condition; wherein said target nerve comprises a nerve originating in an upper cervical spine area of said patient and wherein said medical condition comprises at least one or more of an autoimmune disease, hyperthyroidism, and hypothyroidism."[139]

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[135] Oliver Wendell Holmes, Jr., *The Path of the Law*, 10 HARV. L. REV. 457, 465 (1897). (One can give any conclusion a logical form.) *See also* Brian S. Haney, *Applied Natural Language Processing for Law Practice*, 2020 B.C. Intell. Prop. & Tech. F. 1, 42 (2020). ("As a result, language is often peripheral in the practice of law.")

[136] Sarah Murphy, Heads I Win, Tails You Lose: The "Expense" of a De Novo Review of USPTO Decisions, 60 B.C.L. Rev. II.-197, II.-197 (2019), https://lawdigitalcommons.bc.edu/bclr/vol60/iss9/15. ("The United States Patent and Trademark Office (the "USPTO") may deny patent applications and trademark registrations to applicants who do not meet the necessary requirements.")

[137] M. C. Guardo & K. R. Harrigan, Shaping the path to inventive activity: the role of past experience in R&D alliances, The Journal of Technology Transfer, Springer, vol. 41(2), pages 250-269, (April 2016) DOI: 10.1007/s10961-015-9409-8. ("Not only do they represent an externally validated measure of technological novelty with a clear economic significance, but their correlation with other measures of technological performance, such as new products or innovation counts, has been vetted.")

[138] Stefania Fusco, *Trips Non-Discrimination Principle: Are Alice and Bilski Really The End of NPEs?*, 24 TEX. INTELL. PROP. L.J. 131, 139 (2016), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2653463. ("The accusations were primarily directed at the quality of business method patents and, specifically, the lack of novelty in their inventions.") *See also* Mark A. Lemley & Mark P. McKenna, *Scope*, 57 WM. & MARY L. REV 2197, 2240 (2015). (accessed at https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2660951) ("Because patent law requires that an invention be novel and nonobvious, it should be clear that a patent owner is not entitled to sue someone for using technology that existed before she ever "invented" it.")

[139] U.S. Patent. No. 7,493,172 to Whitehurst, et al., Methods and systems for stimulating a nerve originating in an upper cervical spine area to treat a medical condition (February 17, 2009). (Assigned to Boston Scientific Neuromodulation Corp.)

The claim is a method for treating a medical condition, wherein the medical condition includes an autoimmune or thyroid disease. The claim's novelty is in the applying a stimulus to the nervous system according to pre-defined parameters.

The invention highlights the critical relationship between the thyroid and nervous system.[140] Yet, novelty in thyroid technologies and treatments is not a difficult task to achieve due to the currently shallow limits in human knowledge. In other words, very little is known about the thyroid, providing opportunity for innovation. The backdrop against which something is new is a critical aspect for the novelty requirement. Larissa Bifano, a Partner with DLA Piper explains, "In addition to the technical details, establishing a narrative of the inventive concept can greatly help practitioners during the prosecution stage."[141]

Professor Elona Marku at the University of Cagliari in Italy is developing objective measures for novelty. In fact, they have developed a quality formalism for measuring patent originality, which may be modified to measure novelty.[142] According to Professor Marku, the algorithmic measure "captures the breadth of the technological knowledge bases that have been synthesized in the focal patent and captures the antecedent technology embodied in each

[140] Larry R. Squire, et al., Fundamental Neuroscience 910 (2008). ("Thyroid hormone receptors are located throughout the brain, highlighting their importance in central nervous system development and function.")
[141] Larissa Bifano, et al., Protecting AI technologies through patents: a US guide, 3-4 DLA Piper (2020), https://www.dlapiper.com/en/us/insights/publications/2020/04/a-us-guide-to-protecting-ai-based-inventions/. ("Recent case law and US Patent Office guidance have focused on identifying the technical improvement that results from the artificial intelligence innovation.")
[142] Elona Marku, et al., Quantity at expense of quality? Measuring the effects of "successful" M&A on innovation performance 8 (2020). The originality algorithm may be modified as follows to measure novelty:

$$Novelty_i = 1 - \sum_{j=1}^{n_i} S_{ij}^2$$

where S_{ij} represents the backward citations of patent i that have class code j, out of n_i different patent technology classes during the four-year, pre-acquisition and post- acquisition windows, respectively.

patent."[143] The intuition is that synthesizing divergent ideas is a characteristic for original research.[144]

iii. Scope

A patent's scope depends on the relevant patent's defined protectable rights.[145] The scope question is not limited to validity or infringement.[146] Rather, it refers to a range of patent rights protecting monopoly.[147] Consider U.S. Patent No. 9,980,933, *Thyroid hormone analogs and methods of use*, which claims:

> "1. A method for treating a condition by promoting angiogenesis, wherein the condition is selected from the group consisting of occlusive vascular disease, coronary disease, erectile dysfunction, myocardial infarction, ischemia, stroke, peripheral artery vascular disorders, wound healing and burns, said method comprising the steps of: formulating a polymer into a nanoparticle, wherein the nanoparticle is less than 200 nanometers, wherein the polymer is polyglycolide, polylactide, or a co-polymer thereof; conjugating a thyroid hormone analog to the nanoparticle forming a conjugated thyroid hormone analog; coating a medical device with the conjugated thyroid hormone analog; administering an effective amount of the conjugated thyroid hormone analog to a subject suffering from the condition by inserting the medical device coated with the conjugated thyroid hormone analog into the subject; initiating non-genomic signal transduction pathways at an integrin $\alpha v\beta 3$ surface receptor of a cell by contacting the conjugated thyroid hormone analog with the $\alpha v\beta 3$ surface receptor, said conjugated thyroid hormone analog does not gain entry to the cell's interior."[148]

[143] Elona Marku, et al., Quantity at expense of quality? Measuring the effects of "successful" M&A on innovation performance 8 (2020).
[144] M. C. Guardo & K. R. Harrigan, *Shaping the path to inventive activity: the role of past experience in R&D alliances*, The Journal of Technology Transfer, Springer, vol. 41(2), pages 250-269, (2016), DOI: 10.1007/s10961-015-9409-8.
[145]Mark A. Lemley & Mark P. McKenna, Scope, 57 WM. & MARY L. REV 2197, 2209 (2015). (accessed at https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2660951) (IP regimes require, not just similarity between the defendant's and plaintiff's works, but similarity with respect to the protectable elements.)
[146] Mark A. Lemley & Mark P. McKenna, Scope, 57 WM. & MARY L. REV 2197, 2202 (2015). (accessed at https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2660951) (IP regimes require, not just similarity between the defendant's and plaintiff's works, but similarity with respect to the protectable elements.)
[147] Dan L. Burk & Mark A. Lemley, Policy Levers in Patent Law, 89 VA. L. REV. 1575, 1675 (2003).
[148] U.S. Patent No. 9,980,933, to Mousa, et al., Thyroid hormone analogs and methods of use (May 29, 2018).

This claim has a long preamble, but the general rule is the preamble does not limit claim scope. However, this claim is limited by the preamble due to the specificity with which the condition is described, as a selection from a group.

An alternative analysis may reveal, this claim contains two transitional phrases, consisting and comprising. Typically, comprising[149] is the broadest transitional phrase and consisting of[150] is the narrowest. But this claim is unique because it is arguably two claims. For example, consider if the claim was re-written as one independent claim and one dependent claim:

> "1. A method for treating a condition by promoting angiogenesis, wherein the condition is selected from the group consisting of occlusive vascular disease, coronary disease, erectile dysfunction, myocardial infarction, ischemia, stroke, peripheral artery vascular disorders, wound healing and burns[.]
>
> [2. The method of claim 1, the method] comprising the steps of: formulating a polymer into a nanoparticle, wherein the nanoparticle is less than 200 nanometers, wherein the polymer is polyglycolide, polylactide, or a co-polymer thereof; conjugating a thyroid hormone analog to the nanoparticle forming a conjugated thyroid hormone analog; coating a medical device with the conjugated thyroid hormone analog; administering an effective amount of the conjugated thyroid hormone analog to a subject suffering from the condition by inserting the medical device coated with the conjugated thyroid hormone analog into the subject; initiating non-genomic signal transduction pathways at an integrin $\alpha v\beta 3$ surface receptor of a cell by contacting the conjugated thyroid hormone analog with the $\alpha v\beta 3$ surface receptor, said conjugated thyroid hormone analog does not gain entry to the cell's interior."[151]

In this instance, the independent claim would have a broader scope, where the dependent claim has a narrower scope. However, as the claim is written, as one claim, the claim is exceptionally

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[149] *Mars Inc. v. H.J. Heinz Co*., 377 F.3d 1369, 1376, 71 USPQ2d 1837, 1843 (Fed. Cir. 2004) ("like the term 'comprising,' the terms 'containing' and 'mixture' are open-ended."). *See also Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997) ("Comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.) (*Comprising* means the invention includes but is not limited to the elements identified in the claim.)

[150] PPG Industries v. Guardian Industries, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998). (*Consisting essentially of* limits the scope of a claim to the specified materials or steps and those that do not materially affect the basic and novel characteristics of the claimed invention.)

[151] U.S. Patent No. 9,980,933, to Mousa, et al., Thyroid hormone analogs and methods of use (May 29, 2018).

narrow, limited to only to the exact and specified materials and steps described. Indeed, the general idea is more words mean narrower claims.[152]

Some suggest, patent law has gaps resulting from conceptual separations in patentability, infringement, and defenses.[153] For example, a party may successfully argue a patent claim means one thing in one context, but something totally different in another.[154] For example, one may argue the claim scope is narrow to the examiner and broad to the judge, knowing neither may have knowledge necessary to understanding the underlying invention.[155] Ultimately, scope is a term of art and is best understood as a continuous scale.[156] In other words, whether a claim is broad or narrow is a subjective ascription, often based on relative comparison.[157] As such, data is a critical advantage for the modern firm because data defines the targets to which the claim is compared.

B. Dataset

The Thyroid Patent Dataset was aggregated to contribute the first empirical analysis for patents relating to the thyroid gland's functionality in the Hypothalamic-Pituitary-Thyroid Axis hormonal control loop. The total Thyroid Patent Dataset currently contains data for 627 patents, and is an iteratively evolving, dynamic software.

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[152] Alan C. Marco, et al., Patent Claims and Patent Scope, U.S. Patent and Trademark Office, Economic Working Paper Series, 9 (October 2016), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2844964. ("Further, this process almost always involves adding words to the claim: modifiers, qualifiers, or other details.")
[153] Mark A. Lemley & Mark P. McKenna, Scope, 57 WM. & MARY L. REV 2197, 2240 (2015). (Arguing patent owners can and do exploit these gaps with some regularity. For example, patentees in computer software, have sought broader patent claim interpretation, to the point where many claims are not limited either to a particular computer algorithm or approach or to a particular hardware implementation.)
[154] Mark A. Lemley & Mark P. McKenna, Scope, 57 WM. & MARY L. REV 2197, 2220-2221 (2015).
[155] Eileen M. Herlihy, *The Ripple Effect of Seventh Amendment Decisions on the Development of Substantive Patent Law*, 27 SANTA CLARA COMPUTER & HIGH TECH L.J. 333, 343 (2011).
[156] Brian S. Haney, Quantum Patents, SSRN at 41, 27 B.U. J. SCI. & TECH. L. __ (2021), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3554925. (Forthcoming)
[157] Brian S. Haney, AI Patents: A Data Driven Approach, 19 Chi.-Kent J. Intell. Prop. 407, 462 (2020), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3527154.

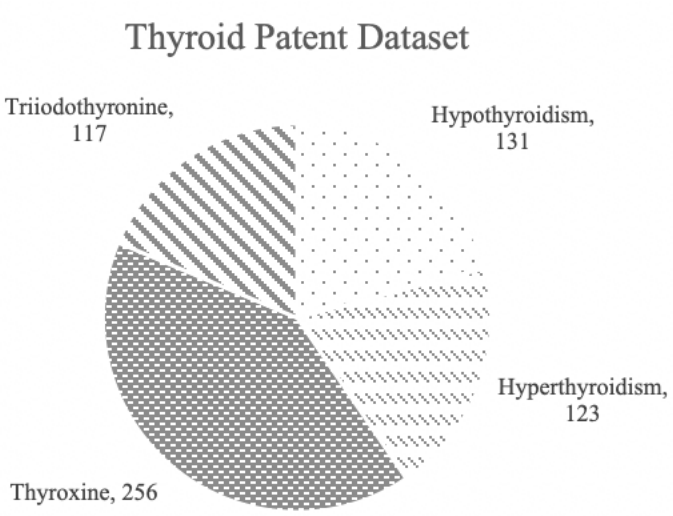

Figure 3[158]

Patents with claims including the two major thyroid diseases, Hypothyroidism (131) and Hyperthyroidism (123) are included in the dataset because they are problems that occur in the Thyroid Control Loop; and the aim for inventions is to solve these problems. Further, patents with claims including the two major thyroid hormones, Thyroxine T_4 (256) and Triiodothyronine T_3 (117) are included in the dataset because they are the effective output for the Thyroid Control Loop.

i. Methods

The Thyroid Patent Dataset is inherently imperfect and incomplete. There are patents relating to the thyroid gland's functionality in the Hypothalamic-Pituitary-Thyroid Axis hormonal control loop, which are not included in the dataset. Additionally, there may be limited overlap in the dataset where patents were counted in more than one category. The main

[158] Brian S. Haney, Thyroid_ Patents (2020). (The information contained in this chart was prepared by the author with information from the United States Patent and Trademark Office.)(A copy of the data is on file with the author.)

assumption is the four terms included in the dataset are representative for broader Thyroid Patent categories.

The dataset is consistently growing with the goal to provide access to key information relating to cures for thyroid disease. The dataset was collected from the USPTO database through structured human techniques in compliance with USPTO policy.[159] Importantly, the USPTO severely restricts public access to patent data, which as a policy must end.[160] The initial terms were selected to pinpoint patents for thyroid disease and thyroid hormone. The dataset is currently limited to patents granted between 1999-2019. The Thyroid Dataset is stored in two formats XLS and CSV for processing.

ii. Analysis

Figure 4 displays analysis performed on the Thyroid Patent Dataset. The analysis focused on three patent metrics associated with patent value, claims, prior art citations, and inventors.

[159] USPTO, *Terms of Use for USPTO Websites* (2020), https://www.uspto.gov/terms-use-uspto-websites. *See also* Veronica Root, *Coordinating Compliance Incentives*, 102 CORNELL L. REV. 1003, 1029 (2017), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2867048. ("Governmental enforcement agencies and actors are also subject to the information and coordination complexities that confront many regulatory agencies within the current administrative state. Importantly, these information and coordination challenges may lead to a responsibility vacuum when considering issues of corporate recidivists.")

[160] *Id*. The USPTO refuses to allow inventors, small business, and researchers access to key patent necessary to promote technical progress and innovation. Instead, the USPTO claims to make data available to the public through a private contract with ReedTech, a Lexis subsidiary. However, the data the USPTO provides in useless for inventors, small businesses, and researchers because it is stored in bulk. As a result, processing the data requires expensive industrial scale computers only accessible to large corporations. This policy could easily be fixed by simply making USPTO data available through a cloud computing model, expanding bandwidth capability and saving money. Yet, resolution is unlikely because the USPTO's financial incentives are to exclude non-corporate entities from the market.

	Claims	Prior Art	Inventors
Count	627.00	627.00	627.00
Mean	25.599681	98.22807	3.103668
Standard Deviation	21.259109	158.23974	2.326491
Minimum	1.00	0.00	1.00
Maximum	183.00	1445.00	22.00
Quartile 1	13.00	16.00	2.00
Quartile 2	20.00	41.00	2.00
Quartile 3	31.00	103.00	4.00
Median	20.00	41.00	2.00
Mode	20.00	12.00	2.00

Figure 4[161]

The analysis was performed with the Python Pandas library,[162] to calculate value properties for the Thyroid Patent Dataset. Data for each patent element was gathered in a separate file and subsequently processed as input to a computer program, which produces statistical results.

iii. Models

Figure 5 depicts analysis for claims[163] in the Thyroid Patent Dataset. One theory is valuable patents contain more claims than ordinary patents.[164] The intuition behind this

[161] Brian S. Haney, Thyroid_ Patents (2020). (The information contained in this chart was prepared by the author with information from the United States Patent and Trademark Office.)(A copy of the data is on file with the author.) Thyroid Patent Informatic Analysis. Python Pandas.
[162] Brian S. Haney, Bhaney44, GitHub, Patent Valuation, Panda_Stats_Thyroid_Patents (2020), https://github.com/Bhaney44/Patent-Valuation/blob/master/Pandas_Stats_Thyroid_Patents.py. (Providing source code for analysis.) *See also* Pandas, Project Description (2020), https://pypi.org/project/pandas/.
[163] Alan C. Marco, et al. Patent Claims and Patent Scope, U.S. Patent and Trademark Office, Economic Working Paper Series, 9 (October 2016), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2844964. (Claims represent the legal bounds of the invention.)
[164] John R. Allison, et al. *Valuable Patents*, 92 GEO. L.J. 435, 438 (2004).

reasoning is consistent with the USPTO fee structure.[165] However, there are exceptions to this theory, where patents with fewer claims are more valuable.

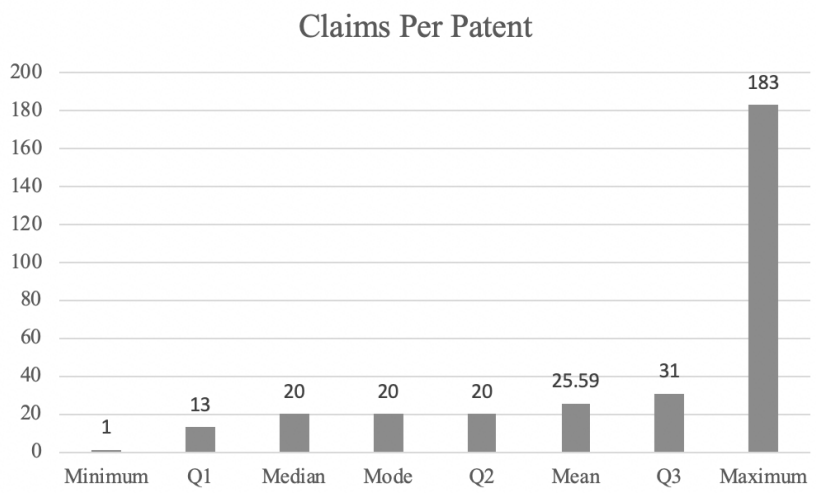

Figure 5[166]

Owned by Ilypsa, Inc., U.S. Patent 8,349,305, *Crosslinked amine polymers*, contained the maximum 183 claims.[167] The minimum was shared by two patents, U.S. Patent 9,550,838, *Dock-and-lock (DNL) complexes for therapeutic and diagnostic use* and U.S. Patent 9,085,510, *Preparation of organic compounds for enhanced reactivity*, each containing 1 claim.[168]

A second theory is valuable patents tend to cite more prior art.[169] This reasoning is commensurate with time and money spent on patent search, research, and drafting – each of

[165] USPTO, USPTO Fee Schedule (2020), https://www.uspto.gov/learning-and-resources/fees-and-payment/uspto-fee-schedule. *See also* Public Law 112-29, Leahy-Smith America Invents Act (September 16, 2011). (See Section 11 fees for patent services, which de facto prevents inventors living in poverty from being able to patent or protect their inventions.)
[166] Brian S. Haney, Thyroid_ Patents (2020). (The information contained in this chart was prepared by the author with information from the United States Patent and Trademark Office.)(A copy of the data is on file with the author.)
[167] U.S. Patent 8,349,305 to Cheng, et al., Crosslinked amine polymers (January 8, 2013).
[168] U.S. Patent 9,550,838, to Chang, et al., Dock-and-lock (DNL) complexes for therapeutic and diagnostic use (January 24, 2017). *See also* U.S. Patent 9,085,510 to Latham, Preparation of organic compounds for enhanced reactivity (July 21, 2015).
[169] John R. Allison, et al. *Valuable Patents*, 92 GEO. L.J. 435, 438 (2004).

which positively corresponds with cost. Figure 6 models the prior art citations for the Thyroid Patent Dataset.

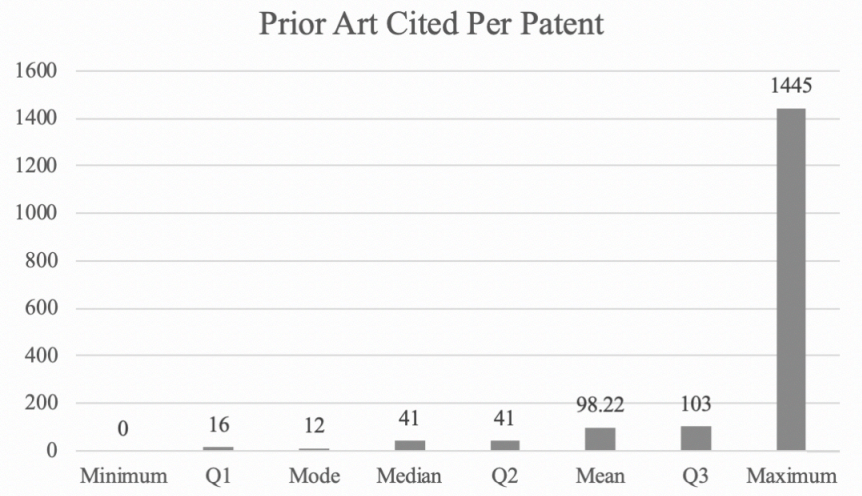

Figure 6[170]

Yet, a contrarian may argue fewer prior art citations are more valuable insofar as the invention is more novel. The minimum in the Thyroid Patent Dataset, owned by The Johns Hopkins University, U.S. Patent No. 9,039,994, *Biomarkers for myocardial ischemia*, cited no prior art.[171] By contrast, the patent with maximum citation count is Owned by SIO2 Medical Products, Inc., U.S. Patent No. 9,662,450, *Plasma or CVD pre-treatment for lubricated pharmaceutical package, coating process and apparatus*, which cited 1,445 prior art.[172]

A third factor which may be considered is a patent's inventorship. A common argument is more inventors and higher inventor prestige corresponds with higher patent quality because more intelligence and time was committed to the patent.[173]

[170] Brian S. Haney, Thyroid_ Patents (2020). (The information contained in this chart was prepared by the author with information from the United States Patent and Trademark Office.)(A copy of the data is on file with the author.)
[171] U.S. Patent No. 9,039,994 to Van Eyk, et al., Biomarkers for myocardial ischemia (May 26, 2015).
[172] U.S. Patent No. 9,662,450 to Jones, et al. Plasma or CVD pre-treatment for lubricated pharmaceutical package, coating process and apparatus (May 30, 2017).
[173] R. Polk Wagner, *Understanding Patent-Quality*, 157 U. PA. L. REV. 2135, 2138 (2009). (Prestige and time may also correlate with the capacity of a granted patent to meet the statutory standards of patentability – most

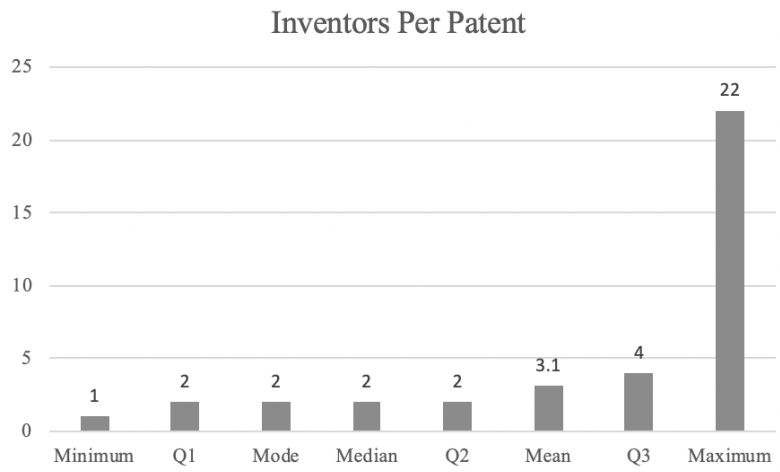

Figure 7[174]

Owned by Otsuka Pharmaceutical Co., U.S. Patent 8,420,623, *N, N-substituted 3-aminopyrrolidine compounds useful as monoamines reuptake inhibitors*, listed twenty-two inventors.[175] However, one counterargument is estimations based on inventorship may overlook inventions by previously unknown inventors which took substantial time and effort. In other words, similar to the way in which politicians attack one another personally rather than underlying policies and ideas, patent valuations based on inventorship fall victim to the *ad hominem* fallacy.[176]

importantly, to be novel, nonobvious, and clearly and sufficiently described.) *See also* Heather Hamel, Valuing the Intangible: Mission Impossible? An Analysis of The Intellectual Property Valuation Process, 5 Cybaris An Intell. Prop. L. Rev. 183, 187 (2014).

[174] Brian S. Haney, Thyroid_ Patents (2020). (The information contained in this chart was prepared by the author with information from the United States Patent and Trademark Office.)(A copy of the data is on file with the author.)

[175] U.S. Patent 8,420,623, to Kurimura, et al., N, N-substituted 3-aminopyrrolidine compounds useful as monoamines reuptake inhibitors, listed twenty-two inventors (April 16, 2013).

[176] The *ad hominem* fallacy refers to logical arguments relating to a person, rather than the position they are maintaining.

C. Calculating Damages

A contentious issue in intellectual property law, patent damages are at the patent policy epicenter.[177] The Patent Act states "[u]pon finding for the claimant the court shall award the claimant damages adequate to compensate for the infringement, but in no event less than a reasonable royalty."[178] In fact, one argument is the reason patents have value is because patents enable the owner to exclude others from the market or receive royalties by licensing the patent.[179] However, a firm's ability to exclude others or collect royalties is dependent on the firm's ability to finance litigation – not on patent rights.

i. Patent Litigation Law

Generally, patent infringement assessment is based on first determining the meaning in each patent claim and second showing the accused infringement meets each claim term.[180] Direct infringement is the broadest clause conferring infringement liability in the Patent Act.[181] In other words, 35 U.S.C. § 271(a) requires the unauthorized use of a patented invention by making, using, offering for sale, selling, or importing the invention.[182] If a patent is found to be valid and infringed, its owner is entitled to infringement damages.[183]

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[177] Jennifer L. Blouin and Melissa F. Wasserman, *Tax Solutions to Patent Damages*, TEX. INTELL. PROP. L.J. (SYMPOSIUM), 2 (2018), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3099060.
[178] 35 U.S.C. § 284 (2015).
[179] Jennifer L. Blouin and Melissa F. Wasserman, *Tax Solutions to Patent Damages*, TEX. INTELL. PROP. L.J. (SYMPOSIUM), 5 (2018), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3099060.
[180] Christopher J. White, Hamid R. Piroozi, Drafting Patent Applications Covering Artificial Intelligence Systems, 11 No. 3 Landslide 10, 14 (2019). (The U.S. Code generally divides infringement in to two categories: direct infringement and indirect infringement.)
[181] 35 U.S.C. § 271(a). ("Except as otherwise provided in this title, whoever without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent therefor, infringes the patent.")
[182] Tabrez Y. Ebrahim, *Dynamicism, Deep Learning, & Patent Theory* (2020) (on file with author)(draft available at https://robots.law.miami.edu/2019/wp-content/uploads/2019/03/Ebrahim_Patent-Infringement.pdf.)
[183] Jennifer L. Blouin and Melissa F. Wasserman, *Tax Solutions to Patent Damages*, TEX. INTELL. PROP. L.J. (SYMPOSIUM), 5 (2018), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3099060.

Courts have interpreted the Patent Act to mean that patent damages come in two primary measures: lost profits and reasonable royalties.[184] Lost profits provide the patentee with the profits the patentee would have made but for the infringing sales as damages in litigation.[185] Proving lost profits, however, is not an easy endeavor.[186] The prevailing patentee must prove: (1) demand for the patented product, (2) a lack of alternatives for the product, (3) the patentee's ability to meet the additional demand, and (4) the foreseeable profits.[187]

Some argue this factually limits lost profit damages awards to "patentees that participate in a market in competition with the infringer."[188] However, this is not correct because meeting the burden for infringement depends on having the financial resources to influence the decision maker.[189] For example, if an inventor or small business with limited financial resources finds a cure for hypothyroidism, any corporation could simply use, make, sell, and profit from the invention without worry because there is highly limited litigation threat.[190]

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[184] Jennifer L. Blouin and Melissa F. Wasserman, *Tax Solutions to Patent Damages*, TEX. INTELL. PROP. L.J. (SYMPOSIUM), 5 (2018), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3099060.
[185] Jennifer L. Blouin and Melissa F. Wasserman, *Tax Solutions to Patent Damages*, TEX. INTELL. PROP. L.J. (SYMPOSIUM), 5 (2018), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3099060.
[186] Jennifer L. Blouin and Melissa F. Wasserman, *Tax Solutions to Patent Damages*, TEX. INTELL. PROP. L.J. (SYMPOSIUM), 5 (2018), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3099060.
[187] *Panduit Corp. v. Stahlin Bros. Fibre Works*, 575 F.2d 1152, 1156 (6th Cir. 1978).
[188] Jennifer L. Blouin and Melissa F. Wasserman, *Tax Solutions to Patent Damages*, TEX. INTELL. PROP. L.J. (SYMPOSIUM), 5 (2018), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3099060. ("Thus, only patentees that participate in a market in competition with the infringer, such as by selling its own product that practices the patent, will be eligible for lost profits damage awards.")
[189] Richard W. Garnett, *Debate: Judicial Activism and its Critics*, 115 U. PENN. L. R. 112, 114 (2006), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=947521. ("I think there is a fairly small set of factors that suggest when courts should defer or should not.") *See also* Richard A. Posner, Theories of Economic Regulation, National Bureau of Economic Research Working Paper No. 41 at 1 (1974). (Economic regulation refers to taxes and subsidies of all sorts as well as to explicit legislative and administrative controls over rates, entry, and other facets of economic activity.)
[190] Tabrez Y. Ebrahim, *Automation & Predictive Analytics in Patent Prosecution: USPTO Implications & Policy*, 35 GA. ST. U. L. REV. 1185, 1194 (2019), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3401250. ("Unlike patent litigation, which is adversarial, the acquisition of patent rights has been considered an iterative negotiation of patent rights between a patent examiner and a patent applicant, who typically begins the negotiation process seeking the broadest possible scope.")

The second measure for damages is reasonable royalties, which are the dominant damages determination.[191] There is general agreement that the discontent with patent damages stems from the reasonable royalty calculation, the most prevalent patent damage award.[192] Today, over 80% of all patent damage awards are reasonable royalties.[193] As such, some describe the Reasonable Royalty Model[194] as a historic bedrock technique in patent license valuation.[195] Courts typically apply a fifteen factor analysis set out in *Georgia-Pacific Corp. v. United States Plywood Corp* to determine reasonable royalty.[196] As such, judicial discretion determines questions relating to conflicting evidence for amount.[197] And, courts inevitably have broad judgment in evaluating the relevant patent value factors.[198]

[191] Jennifer L. Blouin and Melissa F. Wasserman, *Tax Solutions to Patent Damages*, TEX. INTELL. PROP. L.J. (SYMPOSIUM), 6 (2018), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3099060. (Arguing tax-related transfer prices are useful evidence for calculating reasonable royalty patent damages.)
[192] Jennifer L. Blouin and Melissa F. Wasserman, *Tax Solutions to Patent Damages*, TEX. INTELL. PROP. L.J. (SYMPOSIUM), 3 (2018), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3099060.
[193] Jennifer L. Blouin and Melissa F. Wasserman, *Tax Solutions to Patent Damages*, TEX. INTELL. PROP. L.J. (SYMPOSIUM), 6 (2018), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3099060.
[194] Mark A. Lemley, *Distinguishing Lost Profits from Reasonable Royalties*, 51 WM. & MARY L. REV. 655, 669 (2009). (Under a reasonable-royalty model, patent law aims to provide patentees with payment for the "rate that would have both compensated patentees and allowed users of the technology to make a reasonable profit.")
[195] Amy L. Landers, *Patent Valuation Theory and the Economics of Improvement*, 88 TEX. L. REV. 163, 166 (2010). (Patent damages are a make-whole remedy, intended to restore the patentee to the same position as before the infringement. In the context of patent litigation, income models are particularly popular for determining damages.)
[196] Georgia-Pacific Corp. v. United States Plywood Corp., 318 F. Supp. 1116, 1120 (S.D.N.Y. 1970). ("A comprehensive list of evidentiary facts relevant, in general, to the determination of the amount of a reasonable royalty for a patent license may be drawn from a conspectus of the leading cases.")
[197] General Motors Corp. v. Dailey, 93 F.2d 938, 942 (6th Cir. 1937).
[198] Georgia-Pacific Corp. v. United States Plywood Corp., 318 F. Supp. 1116, 1120 (S.D.N.Y. 1970).

ii. Patents are Options

A better way to think about calculating patent damages is with options pricing[199] because option valuations reflect a more diverse and accurate economic information source.[200] Real options theory is used to value intangible assets flexibility.[201] Essentially, the real options approach formalizes intangible asset valuation.[202] For example, a firm can use option pricing to define the value for the ability to legally monopolize a novel cure to hypothyroidism.[203]

Biotechnology patents are options. For example, the option to choose between exclusively commercializing the patented invention or foregoing commercialization altogether.[204] In fact, economists use real options analysis to place specific values on patents.[205] One of the first steps in framing patents as real options is to define the patent's market price.[206]

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[199] Real options are a financial derivatives contract creating the right to purchase an underlying asset at a defined price. Every option has a price and the decisions available to a company can be characterized as real options and defined in terms of value by elements like exercise price or expiration date. There are five key elements for options : (1) A right but not an obligation, (2) at or before some specified time (3) to purchase - a call option, or sell - a put option (4) at a prespecified price - the exercise price (5) an underlying asset whose price is subject to some form of random variation. *See* Nikitas Stamatopoulos, et al., *Option Pricing using Quantum Computers*, 1 (2017), https://arxiv.org/abs/1905.02666. ("Options are financial derivative contracts that give the buyer the right, but not the obligation, to buy (call option) or sell (put option) an underlying asset at an agreed-upon price (strike) and timeframe.") *See also* Andrew Chin, Teaching Patents as Real Options, 95 N.C. L. Rev. 1433, 1441 (2017), http://scholarship.law.unc.edu/nclr/vol95/iss5/4. ("A real option is the right, but not the obligation, to pay a predetermined price to undertake a potentially profitable action in the future.") *See also* Robert Pitkethly, The Value of Patents, Judge Institute Working Paper WP 21/97 (1997), http://users.ox.ac.uk/~mast0140/EJWP0599.pdf.

[200] Christopher A. Cotropia, Describing Patents as Real Options, 34 J. Corp. L. 1127, 1128 (2009).

[201] Christopher A. Cotropia, Describing Patents as Real Options, 34 J. Corp. L. 1127, 1131 (2009).

[202] Christopher A. Cotropia, Describing Patents as Real Options, 34 J. Corp. L. 1127, 1131 (2009).

[203] Christopher A. Cotropia, Describing Patents as Real Options, 34 J. Corp. L. 1127, 1131 (2009).

[204] Maria Isabella Leone, *The Option Value of Patent Licenses*, 2 (2007), https://www.researchgate.net/publication/252398618_The_option_value_of_patent_licenses. (As a consequence, recent attempts in patent valuation efforts have been developed with a real options framework, recognizing uncertainty in patent value.)

[205] Christopher A. Cotropia, Describing Patents as Real Options, 34 J. Corp. L. 1127, 1128 (2009).

[206] A technology's market value is connected to licensing revenues and sales. Importantly, patents are a valuable asset class in information and knowledge economies. This is especially true for high-technology and pharmaceutical companies working in the synthetic life space. *See* Stefania Fusco, The Patentability of Financial Methods: The Market Participants' Perspectives, 45 Loyola of Los Angeles Law Review No. 1 (2011), https://ssrn.com/abstract=1800853. (Discussing the patent and innovation in the financial industry with data analytics compiled through market surveys and interviews.) *See also* Ted Hagelin, A New Method to Value Intellectual Property 30 AIPLA Q.J. 353, 362 (2002).

The patent's filing fees and development costs contribute components for the patent option price.[207]

As such, for Thyroid Patents, options pricing may be valuable due to the need for narrow and specialized skillsets in drafting. Options pricing models also account for costs,[208] profits,[209] and royalties.[210] For example, the option price in a licensing contract for a cure to hyperthyroidism would include the licensee's initial fee to acquire the right to develop, future payments resulting from market exclusivity, and the cost to commercialize the underlying technology.[211]

iii. Standardized Patent Valuation Algorithms

Patent valuation methods are a starting point towards better IP strategy.[212] This Article seeks to advance the literature toward a concrete framework for Thyroid Patent valuation by defining patent value metrics with reference to the state-of-the-art. But, one problem that persists is how to use this information to make better patent strategy decisions. Integrating factors

[207] USPTO, USPTO Fee Schedule (2020), https://www.uspto.gov/learning-and-resources/fees-and-payment/uspto-fee-schedule. *See also* Public Law 112-29, Leahy-Smith America Invents Act (September 16, 2011). (See Section 11 fees for patent services, which de facto prevents inventors living in poverty from being able to patent or protect their inventions.)

[208] Christopher A. Cotropia, *Describing Patents as Real Options*, 34 J. Corp. L. 1127, 1135 (2009).

[209] Maria Isabella Leone, The Option Value of Patent Licenses, 5 (2007), https://www.researchgate.net/publication/252398618_The_option_value_of_patent_licenses. (And, the net present value for a patent license is subject to volatility stemming from different sources of uncertainty. Thus, licensing contracts provide the licensee with the opportunity to acquire the cash flows from the commercialization of the patented technology.)

[210] Andrew Chin, *Teaching Patents as Real Options*, 95 N.C. L. Rev. 1433, 1443 (2017), http://scholarship.law.unc.edu/nclr/vol95/iss5/4. (Most research focuses on the Black-Scholes-Merton model for options pricing. The Black-Scholes-Merton model is based on simplifying assumptions about the statistical movement of stock prices and market efficiency.)

[211] Maria Isabella Leone, The Option Value of Patent Licenses, 5 (2007), https://www.researchgate.net/publication/252398618_The_option_value_of_patent_licenses.

[212] Robert Pitkethly, The Value of Patents, Judge Institute Working Paper WP 21/97 (1997). See also Fusco, Stefania Fusco, The Patentability of Financial Methods: The Market Participants' Perspectives, 45 Loyola of Los Angeles Law Review No. 1 (2011), https://ssrn.com/abstract=1800853. (Discussing the patent and innovation in the financial industry with data analytics compiled through market surveys and interviews.) *See also* Stefania Fusco, et al., Monetization Strategies of University Patents Through PAEs: an Analysis of US Patent Transfers, ISSI Conference Proceedings (2019), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3410086.

correlating with patent value with an expert system provides a solution formalizing the decision process. Two ways in which an expert system may be developed are with a V-Score Valuation and a B-Score Valuation.

One method is to apply a V-Score patent valuation algorithm to dataset.[213] V-scores may be particularly efficacious in forecasting the content of firms' organizational learning because of how they characterize changes in firms' technology trajectories.[214] The V-Score uses three value measures (1) technological diversity, (2) technology distance from patent antecedents, and (3) novelty per each patented innovation."[215] Second, B-Score Valuation provides a method for simpler valuation, driven by market economics. The B-Score formalizes human intuition in decision making by integrating an intelligent system with a value function.[216] Defining value factors diversely allows the B-Score valuation to account for a heterogenous factor array with arbitrary length.

While patent valuation is inherently subjective, standardized valuation algorithms provide a method to more objectively measure patent value for calculating damages, flexibly combining

[213] Kathryn Rudie Harrigan, et al., Using a distance measure to operationalize patent originality (2016), https://doi.org/10.1080/09537325.2016.1260106.

$$V = \left[\left[\sum_{k=1}^{n_i} f_i\right] + \left[\sum_{k=1}^{m_o} f_0\right] \times \left[\left[\sum_{j=1}^{n_i} p_{ij} \,/\, i_n\right] + \left[\sum_{j=1}^{m_o} p_{oj} \,/\, o_m\right]\right] \times \left[\sum_{o=1}^{m} f_o \,/\, \sum_{i=1}^{n} f_i\right]\right]$$

[214] Kathryn Rudie Harrigan, et al., Using a distance measure to operationalize patent originality (2016) https://doi.org/10.1080/09537325.2016.1260106. *See also* Kathryn Rudie Harrigan, Maria Chiara Di Guardo, Elona Marku, Patent value and the Tobin's q ratio in media services (2017).

[215] Kathryn Rudie Harrigan, Maria Chiara Di Guardo, Elona Marku & Brian Nicholas Velez, Using a distance measure to operationalize patent originality 992 (2016), https://doi.org/10.1080/09537325.2016.1260106. ("The three terms correspond to measures of (1) technological diversity, (2) technology distance from patent antecedents, and (3) degree of novelty per each patented innovation.")

[216] Formally the B-Score's value function is defined:

$$B = \frac{\prod_{i=1}^{n} F_i}{n}$$

objective metrics. Still no dogma exists for technology valuation.[217] The aim in valuing patents is to enable the public to sufficiently and accurately value patents and inform decision making concerning intellectual property.[218] For example, an investor making a decision about whether to purchase stock in a public company advertising a cure to hypothyroidism needs to know whether the cure has been legally monopolized. Alternatively, a startup developing new endocrinology technologies needs to know how much the company's IP is worth when seeking outside investment capital.

Conclusion

From a legal perspective, Thyroid IP protection strategy is evolving to include new thought streams like open source information and proprietary trade secrets. The open-source strategy is unique because companies make IP publicly available.[219] In the globalized economy, this strategy makes sense in certain circumstances where there are strong reasons to let others access IP.[220] Another strategy is trade secrets. Generally, trade secrets include formulas, patterns, programs, devices, methods, techniques, and processes.[221] The traditional balance between

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[217] Amy L. Landers, *Patent Valuation Theory and the Economics of Improvement*, 88 TEX. L. REV. 163, 165 (2010). *See also* Stefania Fusco, et al., Monetization Strategies of University Patents Through PAEs: an Analysis of US Patent Transfers, ISSI Conference Proceedings (2019), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3410086. (Discussing the US Patent Assignment Dataset which allows for identifying patent transfers registered at the USPTO.)

[218] Robert Pitkethly, The Value of Patents, Judge Institute Working Paper WP 21/97 (1997). (For example, to decide how much to pay for or invest in a business as part of the firms overall financial planning.)

[219] JOHN PALFREY, INTELLECTUAL PROPERTY STRATEGY 105 (MIT Press 2012). *See also Junger v. Daley*, 209 F.3d 481 (6th Cir. 2000). (The Sixth Circuit held that all source code is First Amendment speech because of its expressiveness in conveying ideas about computer programming.)

[220] Importantly, in open source models the creator does not give away all the rights free and information may be disguised or limited. *See* Jeanne C. Fromer, *Machines as the New Oompa-Loompas: Trade Secrecy, the Cloud, Machine Learning, and Automation*, N.Y.U. L.R., 706, 717 (2019), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3359746. ("Contractual restrictions on disclosure and reverse engineering diminish an otherwise critical intrinsic weakness of trade secrecy for software: software's openness to independent discovery and reverse engineerability.")

[221] Trade Secret, Black's Law Dictionary (10th ed. 2014). *See also* Gavin C. Reid, et al., What's it Worth to Keep a Secret?, 13 DUKE L. & TECH. REV. 116, 129 (2015). (Arguing firms opting to utilize the trade secret approach are able to employ relatively straight forward strategies, where the objective function is to minimize the sum of (1) the expected loss due to trade secret dissipation, and (2) the cost of implementing preventative procedures for the protection of trade secrets.)

patents and trade secrets describes patent disclosure as a dismantling drawback.[222] All the while, trade secrets have advantages.[223] For example, trade secret protections are immediate, while it takes years to get a patent.[224]

From a technical standpoint,[225] the human Thyroid's future will be defined by synthetic intelligence. For example, machine learning[226] is a form of data analysis that uses algorithms to continuously learn from data by recognizing hidden patterns without being programmed to do so.[227] Machine learning techniques accelerate drug discovery,[228] diagnostics,[229] and materials design.[230] Finally, the ultimate goal is an intelligent synthetic thyroid, manufactured for human metabolic control flow optimization.

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[222] Mark A. Lemley, The Surprising Virtues of Treating Trade Secrets as IP Rights, 61 STAN. L. REV. 311, 326 (2008). (Trade secret law confers an exclusive right on the possessor of valuable information not generally known to competitors.) *See also* Gavin C. Reid, et al., What's it Worth to Keep a Secret?, 13 DUKE L. & TECH. REV. 116, 129 (2015). (Trade secret law allows firms to protect their proprietary technologies and without publicly disclosing sensitive firm information.)

[223] Jeanne C. Fromer, *Machines as the New Oompa-Loompas: Trade Secrecy, the Cloud, Machine Learning, and Automation*, N.Y.U. L.R., 706, 710 (2019), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3359746. ("Although misappropriation can take various forms, the most common types are acquisition, use, or disclosure of another's trade secret by 'improper means' or by a person with 'a duty to maintain its secrecy or limit its use.'")

[224] Mark A. Lemley, The Surprising Virtues of Treating Trade Secrets as IP Rights, 61 STAN. L. REV. 311, 326 (2008).

[225] Samantha Zyontz, Making the Cut: The Rate and Direction of CRISPR Innovation (2019) https://dspace.mit.edu/handle/1721.1/123571. ("For technological progress, innovators not only need knowledge in a field of study, but also require tools. The interplay between field knowledge and new tools leads to an ever-expanding base from which innovation emerges.")

[226] Emily Berman, *A Government of Laws and Not of Machines*, 98 B.U. L. REV. 1277, 1278 (2018), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3098995. (Machine learning is a strand of artificial intelligence that sits at the intersection of computer science, statistics, and mathematics, and it is changing the world.) *See also* Jeanne C. Fromer, *Machines as the New Oompa-Loompas: Trade Secrecy, the Cloud, Machine Learning, and Automation*, N.Y.U. L.R., 706, 708 (2019), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3359746. ("As this Article describes, at least three recent shifts in the computing industry—cloud computing, the increasing primacy of data and machine learning, and automation— have turned these machines into the new Oompa-Loompas.")

[227] Tabrez Y. Ebrahim, *Computational Experimentation*, 21 VAND. J. OF ENT. &T.L. 591, 602 (2019), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3369945. ("Machine learning is simply a form of data analysis that uses algorithms to continuously learn from data by recognizing hidden patterns without being programmed to do so.")

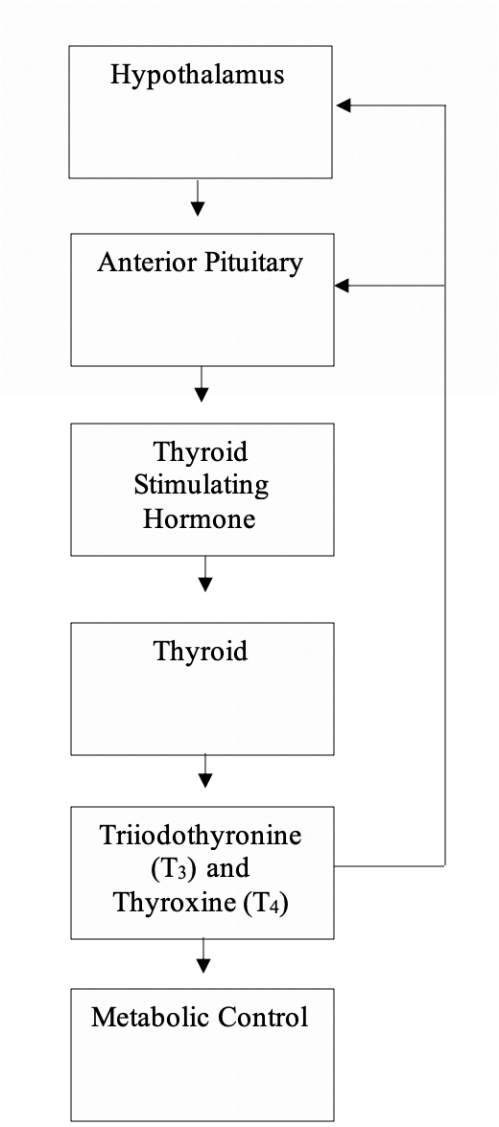
[228] Tabrez Y. Ebrahim, *Computational Experimentation*, 21 VAND. J. OF ENT. &T.L. 591, 603 (2019), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3369945.

[229] Ava P. Soleimany, Activity-Based Diagnostics: An Emerging Paradigm for Disease Detection and Monitoring, 1 (2020), https://doi.org/10.1016/j.molmed.2020.01.013. ("Accurate detection and diagnosis of disease are essential for effective clinical management and treatment.")

[230] Simone Schuerle, et al., Three-Dimensional Magnetic Manipulation of Micro- and Nanostructures for Applications in Life Sciences (2013), https://ieeexplore.ieee.org/document/6392417.

Appendices

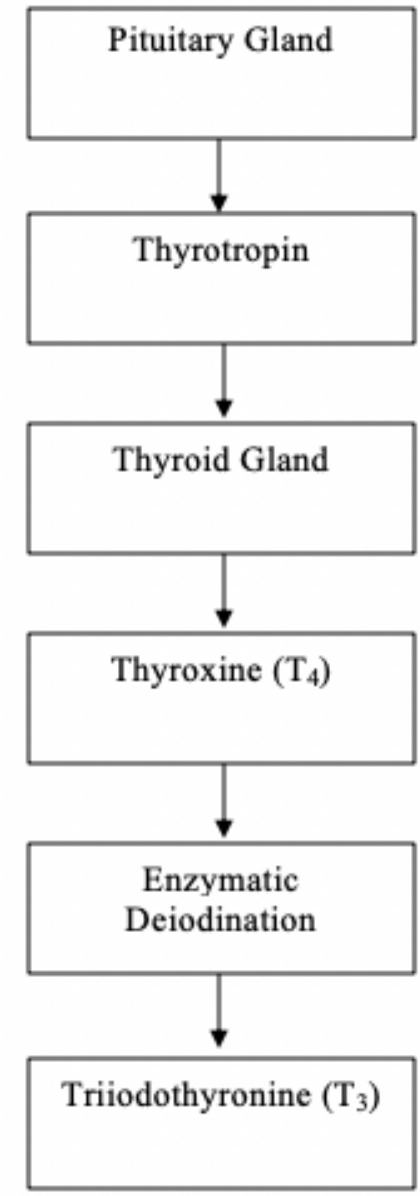
Appendix A. Hypothalamic-Pituitary-Thyroid Axis Model



Appendix B. Hypothalamic-Pituitary-Thyroid Axis Description

Element	Description
Hypothalamus	The link between the endocrine and nervous system, the Hypothalamus is responsible for producing hormones.
Anterior Pituitary	A glandular lobe which secretes thyroid hormone and is located in the located in the pituitary gland.
Thyroid Stimulating Hormone	A pituitary hormone stimulating the thyroid gland to produce Triiodothyronine T_3 and Thyroxine T_4.
Thyroid	The thyroid is a bilobal gland located at the base of the neck producing hormones that regulate body metabolism and organ function.
Triiodothyronine T_3	A thyroid hormone.
Thyroxine T_4	A thyroid hormone.
Metabolic Control	Metabolism refers to the chemical reactions necessary for life, the control of which results from endocrine processes.

Appendix C. Thyroid Hormone Flow Model



Appendix D. Levothyroxine Tablet Information

Name	Manufacturers	Inactive Ingredients
Unithroid	Jerome Stevens Pharmaceuticals	Acacia, colloidal silicon dioxide, corn starch, lactose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate
Synthroid	AbbVie	Acacia, Confectioner's sugar, corn starch, lactose monohydrate, magnesium stearate, povidone, talc
Levoxyl	Pfizer King Pharmaceuticals	Calcium sulfate dehydrate, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, sodium bicarbonate
Levo-T	Cediprof	Magnesium stearate, microcrystalline cellulose, colloidal silicone dioxide, sodium starch glycolate
Euthyrox	Merck	Citric acid anhydrous, corn starch, gelatin, magnesium stearate, mannitol, sodium croscarmellose
Generic Levothyroxine Sodium	Mylan	Butylated hyrdoxyanisole, colloidal silicon dioxide, crospovidone, ethyl alcohol, magnesium stearate, mannitol, microcrystalline cellulose, povidone, sodium lauryl sulfate, sucrose