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## Inventions and Patents for Treating Thyroid Disease

### 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, psychosis, and heart disease. Yet, while the healthcare law scholarship is visibly scaling, the research relating to law, innovation, and thyroid disease is completely naked. This Article provides an interdisciplinary introduction to the Thyroid Patent Dataset, an evolving mechanism for tracking progress in treatments for thyroid disease and advances the literature in providing the first consolidated review of patents for a specific disease. In short, this Article explores the confluence of thyroid disease, patent law, and innovation policy to promote knowledge in human health relating to the human thyroid.

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## Introduction

One in six people have thyroid disease in their lifetime. Most people who have thyroid disease do not know they have it because symptoms are not specific, and it is difficult to isolate in diagnostics.<sup>2</sup> Still, second only to diabetes, thyroid diseases are the most ubiquitous endocrine disorders worldwide.<sup>3</sup> Although thyroid diseases may be life lasting and terminal, they are generally considered treatable.<sup>4</sup>

The thyroid is a bilobal gland located at the base of the neck in front of the windpipe.<sup>5</sup> The thyroid's functionality is essentially synthesizing thyroid hormone.<sup>6</sup> In other words, the thyroid produces hormones, which are secreted into the blood and control the body's metabolism.<sup>7</sup> Interestingly, thyroid hormone receptors are located throughout the brain, highlighting their importance in central nervous system's development and function.<sup>8</sup>

This Paper proceeds in three parts. Part I explores thyroid disease, including diagnostics, hypothyroidism, and hyperthyroidism. Part II empirically investigates inventions for treatments to thyroid disease through the lens of the patent system. Part III consolidates considerations for commercialization of inventions for treating thyroid disease. The purpose for this paper is advancing the literature and human knowledge in thyroid disease, intellectual property, and invention commercialization.

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<sup>2</sup> 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. Abnormal biochemical thyroid function reports substantiate substantial populations suffer from subclinical conditions.

<sup>3</sup> 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>.

<sup>4</sup> 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>.

<sup>5</sup> U.S. Patent No. 6,740,680 to Danforth, Jr., et al., Pharmaceutical compositions to tetrac and methods of use thereof (May 25, 2004).

<sup>6</sup> 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.”)

<sup>7</sup> Hypothyroidism, American Thyroid Association, 4 (2013), [https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism\\_web\\_booklet.pdf](https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf).

<sup>8</sup> 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.)

## I. Thyroid Disease

Thyroid hormone synthesis and release is a three-step process feedback loop.<sup>9</sup> First, the hypothalamus produces Thyroid Releasing Hormone (TRH),<sup>10</sup> stimulating the pituitary gland<sup>11</sup> to release Thyroid Stimulating Hormone (TSH), Thyrotropin,<sup>12</sup> which in turn activates the thyroid gland. Second, the thyroid gland excretes two thyroid hormones: Thyroxine (T<sub>4</sub>) and Triiodothyronine (T<sub>3</sub>) to the bloodstream.<sup>13</sup> Third, T<sub>4</sub> converts to T<sub>3</sub> through deiodination in peripheral tissues.<sup>14</sup> This synthesis is critical for metabolic control in the human body.<sup>15</sup>

Thyroid disease control is extremely essential, and abnormalities can have catastrophic consequences.<sup>16</sup> Thyroid hormone imbalance can have profound effects on the central nervous system, heart, and brain.<sup>17</sup> Indeed, T<sub>3</sub> and T<sub>4</sub> also provide feedback to the brain and anterior pituitary gland to regulate TRH and TSH.<sup>18</sup> Subclinical conditions have subtle manifestations and may mimic other diseases.<sup>19</sup> And, among patients taking thyroid medication, only 60% were within the normal range of TSH.<sup>20</sup> In short, modest TSH fluctuations corresponded to

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<sup>9</sup> 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>.

<sup>10</sup> 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.)

<sup>11</sup> 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.)

<sup>12</sup> Thyrotrope cells in the pituitary gland produce a glycoprotein hormone called thyrotropin, which regulates endocrine function.

<sup>13</sup> 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>.

<sup>14</sup> 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).

<sup>15</sup> See Appendix A for Thyroid Control Loop.

<sup>16</sup> 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.)

<sup>17</sup> Larry R. Squire, et al., Fundamental Neuroscience 912 (2008).

<sup>18</sup> 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.)

<sup>19</sup> 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>.

<sup>20</sup> 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.

physiological changes affecting patient health.<sup>21</sup> Thyroid dysfunction is common, often undetected, and may be associated with adverse health outcomes.<sup>22</sup>

Identifying thyroid disease is challenging because symptoms often develop so subtly that they go unnoticed.<sup>23</sup> The difficulty with many studies lies in the variable disease state definitions, where poorly defined populations are studied with limited thyroid functional measures.<sup>24</sup> Additionally, studies from various countries differ in their estimates for both hypothyroidism and hyperthyroidism.<sup>25</sup>

Thyroxine (T<sub>4</sub>) 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.<sup>26</sup> Distinctly, Thyroxine T<sub>4</sub> contains four iodine atoms per molecule.<sup>27</sup>

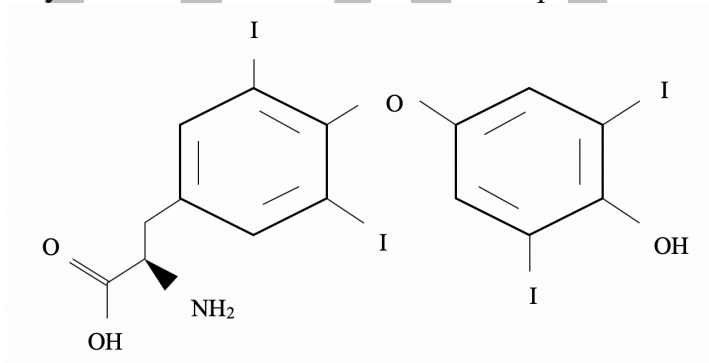


Figure 1<sup>28</sup>

<sup>21</sup> 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.

<sup>22</sup> 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.

<sup>23</sup> 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.

<sup>24</sup> 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.”)

<sup>25</sup> 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.

<sup>26</sup> Michelle So, et al., Hypothyroidism: Investigation and management, 41 Australian Family Physician 556, 559 (2020), <https://www.racgp.org.au/afp/2012/august/hypothyroidism/>.

<sup>27</sup> 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](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<sub>4</sub> because it contains four iodine molecules.)

<sup>28</sup> Thyroxine Molecule.

As blood flows through the pituitary gland, cells measure  $T_4$  levels to determine set point accuracy.<sup>29</sup> The pituitary cells communicate with the thyroid through TSH secretion.<sup>30</sup>

When  $T_4$  levels are at a set point,<sup>31</sup> the pituitary gland sends out enough TSH to tell the thyroid to maintain homeostasis.<sup>32</sup> If the  $T_4$  levels get low, the pituitary gland releases more TSH, telling the thyroid to make more  $T_4$ .<sup>33</sup> Conversely if  $T_4$  are high, the pituitary gland releases less TSH to slow production.<sup>34</sup> For some patients, Thyroxine replacement may be beneficial where TSH levels are elevated however, this remains controversial.<sup>35</sup> Indeed,  $T_3$  has greater biological activity than  $T_4$  comparatively.<sup>36</sup>

$T_4$  converts to the active Triiodothyronine ( $T_3$ ) within cells and peripheral tissues by deiodinases.<sup>37</sup> As such, in contrast to  $T_4$ , the  $T_3$  molecule contains three iodine atoms.<sup>38</sup>

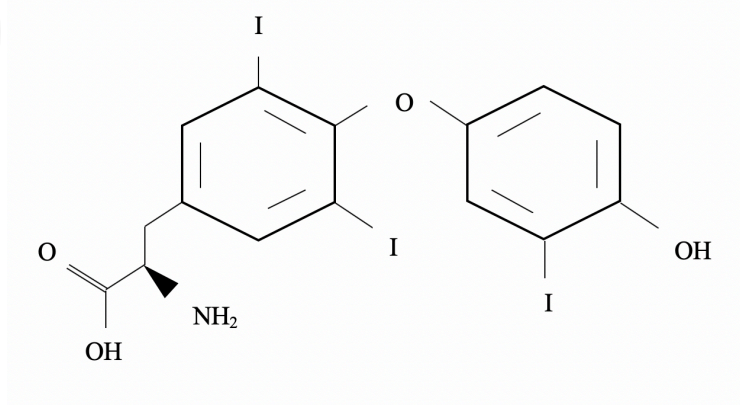


Figure 2<sup>39</sup>

<sup>29</sup> Hypothyroidism, American Thyroid Association, 10 (2013), [https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism\\_web\\_booklet.pdf](https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf).

<sup>30</sup> Hypothyroidism, American Thyroid Association, 10 (2013), [https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism\\_web\\_booklet.pdf](https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf).

<sup>31</sup> A set point is a predetermined hormone level.

<sup>32</sup> Hypothyroidism, American Thyroid Association, 10 (2013), [https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism\\_web\\_booklet.pdf](https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf).

<sup>33</sup> Hypothyroidism, American Thyroid Association, 10 (2013), [https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism\\_web\\_booklet.pdf](https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf).

<sup>34</sup> 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.”)

<sup>35</sup> Michelle So, et al., Hypothyroidism: Investigation and management, 41 Australian Family Physician 556, 561 (2020), <https://www.racgp.org.au/afp/2012/august/hypothyroidism/>.

<sup>36</sup> Larry R. Squire, et al., Fundamental Neuroscience 911 (2008).

<sup>37</sup> 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  $T_3$ .)

<sup>38</sup> 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>.

<sup>39</sup> Triiodothyronine Molecule.

T<sub>3</sub> is the physiologically active thyroid hormone.<sup>40</sup> It controls myocardium properties, heart rate, and vascular function.<sup>41</sup> In fact, T<sub>3</sub> affects almost every process in the body.<sup>42</sup>

Interestingly, one report suggests the thyroid gland produces T<sub>3</sub> directly.<sup>43</sup> Although, thyroid disease is typically not treated with T<sub>3</sub> supplementation. However, some researchers speculate a T<sub>4</sub> and T<sub>3</sub> combination might be better.<sup>44</sup> Molecular structures are important because clinical effects resulting from thyroid hormone imbalance are observable at the cellular level.<sup>45</sup> Thyroid diseases are influenced by endocrine physiology, particularly where abnormal thyroid hormone concentrations affect organ function resulting in clinical symptoms.<sup>46</sup>

## A. Hypothyroidism

Hypothyroidism is a “commonly clinically diagnosed condition describing a thyroid hormone deficiency.”<sup>47</sup> If left untreated, hypothyroidism can lead to serious adverse health effects on multiple organ systems, with the cardiovascular system as the most robustly studied target.<sup>48</sup> An estimated 2% – 3% of Americans have clinical hypothyroidism and 10% – 15% have sub-clinical hypothyroidism.<sup>49</sup> 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.<sup>50</sup> And, approximately 10% – 15% of patients with hypothyroidism display significant psychological impairment.<sup>51</sup>

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<sup>40</sup> 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<sub>3</sub> is the biologically active form of the hormone, most T<sub>3</sub> in the brain is formed from local deiodination of T<sub>4</sub>; thus, T<sub>3</sub> replacement is not needed for normal neurologic functioning.)

<sup>41</sup> 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>.

<sup>42</sup> 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>.

<sup>43</sup> 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.)

<sup>44</sup> Hypothyroidism, American Thyroid Association, 17 (2013), [https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism\\_web\\_booklet.pdf](https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf).

<sup>45</sup> 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>.

<sup>46</sup> 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>.

<sup>47</sup> Hypothyroidism, Nature Reviews Disease Primers volume 8, Article number: 30 (2022).

<sup>48</sup> Hypothyroidism, Nature Reviews Disease Primers volume 8, Article number: 30 (2022).

<sup>49</sup> Hypothyroidism, American Thyroid Association, 4 (2013), [https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism\\_web\\_booklet.pdf](https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf).

<sup>50</sup> Hypothyroidism, American Thyroid Association, 4 (2013), [https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism\\_web\\_booklet.pdf](https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf).

<sup>51</sup> 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>.

There are several types of hypothyroidism. For example, Congenital Hypothyroidism (CH) is defined as thyroid hormone deficiency present at birth.<sup>52</sup> CH describes an organism with insufficient thyroid hormone during early neonatal development.<sup>53</sup> Thyroid hormone deficiency at birth is most caused by a problem with the gland's physical development or impaired thyroid hormone biosynthesis.<sup>54</sup>

A second example is autoimmune hypothyroidism, which is characterized by elevated serum TSH with reduced Free T<sub>4</sub> levels, serum antibodies against thyroid antigens, and reduced echogenicity in the thyroid sonogram.<sup>55</sup> In fact, thyroid autoimmunity is one of the most common causes of hypothyroidism, Hashimoto's disease.<sup>56</sup> Hashimoto thyroiditis is also impacted by environmental factors including vitamin D and selenium deficiency, and moderate alcohol intake.<sup>57</sup>

Hypothyroidism, has several causes.<sup>58</sup> For example, the thyroid must have iodine to make thyroid hormone.<sup>59</sup> Too much iodine may also cause and worsen hypothyroidism.<sup>60</sup> In the Western World, hypothyroidism is most caused by autoimmune chronic lymphocytic thyroiditis.<sup>61</sup> However, worldwide, iodine deficiency is the most common cause for hypothyroidism, although it is a rare cause in the U.S.<sup>62</sup>

Hypothyroid symptoms include anxiety, weakness, heart disease, constipation, depression, and weight gain.<sup>63</sup> Further, many patients report ongoing symptoms such as muscle aching and

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<sup>52</sup> Rastogi, M.V., LaFranchi, S.H. Congenital hypothyroidism, 5 Orphanet J. Rare Disease, 1 (2010), <https://doi.org/10.1186/1750-1172-5-17>.

<sup>53</sup> Larry R. Squire, et al., Fundamental Neuroscience 912 (2008).

<sup>54</sup> 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.")

<sup>55</sup> 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>.

<sup>56</sup> 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.")

<sup>57</sup> Hypothyroidism, Nature Reviews Disease Primers volume 8, Article number: 30, 2 (2022).

<sup>58</sup> U.S. Patent No. 6,740,680 to Danforth, Jr., et al., Pharmaceutical compositions to tetrac and methods of use thereof (May 25, 2004).

<sup>59</sup> Hypothyroidism, American Thyroid Association, 8 (2013), [https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism\\_web\\_booklet.pdf](https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf).

<sup>60</sup> Hypothyroidism, American Thyroid Association, 8 (2013), [https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism\\_web\\_booklet.pdf](https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf).

<sup>61</sup> 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.")

<sup>62</sup> Hypothyroidism, American Thyroid Association, 8 (2013), [https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism\\_web\\_booklet.pdf](https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf).

<sup>63</sup> 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>.



tiredness.<sup>64</sup> Additionally, hypothyroidism is more common in biological females than biological males, and more common in the elderly than young.<sup>65</sup> In fact, most disease related deficiencies can be mitigated by newborn infant screening and thyroid hormone replacement.<sup>66</sup> Still, a completely unsupported, yet pervasive claim in modern medicine is hypothyroidism cannot be cured.<sup>67</sup> But, the truth is whether we think we can or we think we can't; we're probably right.

## B. Hyperthyroidism

Hyperthyroidism describes an excess thyroid hormone causing the pituitary gland to produce less TSH.<sup>68</sup> TSH measurement is the base for the hyperthyroidism diagnosis.<sup>69</sup> In short, low TSH and high T<sub>3</sub> and T<sub>4</sub> corresponds to hyperthyroidism.<sup>70</sup> Thyroid gland overactivity has several causes.<sup>71</sup> Hyperthyroidism symptoms include sweating, heart palpitations, and weight loss.<sup>72</sup> Additional symptoms include increased body temperature, decreased body weight, decreased serum cholesterol, increased stroke volume, and arrhythmia.<sup>73</sup> Excessive thyroid hormone, can also result in symptoms such as tremor, nervousness, insomnia, and impairments in memory and concentration.<sup>74</sup>

Hyperthyroidism is characterized by excessive secretion of thyroid hormones; the most common cause is the autoimmune disorder Graves' disease.<sup>75</sup> Graves' hyperthyroidism is a hypermetabolic state, affecting virtually every tissue and cell in the body and leads to cardiovascular dysfunction

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<sup>64</sup> 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>.

<sup>65</sup> 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.”)

<sup>66</sup> 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.”)

<sup>67</sup> Hypothyroidism, American Thyroid Association, 12 (2013), [https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism\\_web\\_booklet.pdf](https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf).

<sup>68</sup> 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>.

<sup>69</sup> 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>.

<sup>70</sup> U.S. Patent No. 6,740,680 to Danforth, Jr., et al., Pharmaceutical compositions to tetrac and methods of use thereof (May 25, 2004).

<sup>71</sup> U.S. Patent No. 6,740,680 to Danforth, Jr., et al., Pharmaceutical compositions to tetrac and methods of use thereof (May 25, 2004).

<sup>72</sup> 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>.

<sup>73</sup> 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.)

<sup>74</sup> Larry R. Squire, et al., Fundamental Neuroscience 912 (2008).

<sup>75</sup> U.S. 9,206,154, to Gershengorn, et al., Inverse agonists and neutral antagonists for the TSH receptor (December 8, 2015).

and death.<sup>76</sup> Graves' hyperthyroidism is treated by surgical resection,<sup>77</sup> therapeutic doses of radioactive iodine, or pharmacologically.<sup>78</sup> However, each of these treatment modalities has side effects associated with it.<sup>79</sup> Often, both Hypothyroidism and Hyperthyroidism are treatable with lifelong synthetic thyroid hormone replacement.<sup>80</sup> Part II explores thyroid disease through the patent system and the development of legal claims to new inventions for treating thyroid disease.

### C. Diagnostics

Diagnostics refers to the process by which disease is identified. For patients, diagnosis of thyroid disease is often conducted through a combination of patient symptoms and biochemical testing of thyroid function.

Measure	Normal Range
free T3	2.2-4.2 PG/ML
free T4	0.80-1.90 NG/DL
ultrasensitive TSH	0.40-4.10 UIU/ML
thyroglobulin	1.3-31.8 ng/mL

Table 1

There are two primary immunoassays used to diagnose thyroid dysfunction. First, TSH levels are measured. If levels do not fall within normal range, circulating free forms of T3 and T4 in patient blood are measured. TPOAb or anti-thyroglobulin antibodies are also markers used to detect thyroid autoimmunity.<sup>81</sup>

Disease	Symptoms	Common Symptoms
Hypothyroidism	37	Fatigue; sensitivity to cold; weight gain; constipation.
Hyperthyroidism	30	Nervousness; anxiety; sleep problems; weight loss.

Table 2<sup>82</sup>

<sup>76</sup> 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.)

<sup>77</sup> Hypothyroidism, American Thyroid Association, 7 (2013), [https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism\\_web\\_booklet.pdf](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.”)

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

<sup>79</sup> U.S. 9,206,154, to Gershengorn, et al., Inverse agonists and neutral antagonists for the TSH receptor (December 8, 2015).

<sup>80</sup> U.S. Patent No. 6,740,680 to Danforth, Jr., et al., Pharmaceutical compositions to tetrac and methods of use thereof (May 25, 2004).

<sup>81</sup> Hypothyroidism, Nature Reviews Disease Primers volume 8, Article number: 30 (2022). See also Layal Chaker, et. al., Hashimoto's thyroiditis: TGAb, TPOAb, TRAb and recovery from hypothyroidism (May 19, 2022).

<sup>82</sup> Appendix D.

Depending on abnormalities and other symptoms, patients may be diagnosed with a variety of thyroid diseases, including thyroid cancer,<sup>83</sup> hypothyroidism, and hyperthyroidism.

## II. Inventions and Patents

A patent<sup>84</sup> is a form of legal protection for new and useful technologies.<sup>85</sup> It provides the holder the legal right to prohibit others from using, making, or selling an invention.<sup>86</sup> Notre Dame Law Professor Stephen Yelderman argues the U.S. patent system's central goal is to provide adequate incentive to innovators to publish their invention in exchange for rights.<sup>87</sup> However, practically speaking the United States Patent Office has largely abandoned this goal and instead focuses on stopping technical progress and promoting stagnation by reviewing applications from large companies fast and simply ignoring inventions filed by small businesses and inventors for many years despite being grossly overfunded and overstaffed.<sup>88</sup> As such, in conferring the exclusive right to discoveries to its inventors, patents confer a temporary monopoly to the holder.<sup>89</sup>

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<sup>83</sup> The four main kinds of thyroid cancer are papillary, follicular, medullary, and anaplastic. However, thyroid cancer is relatively far rarer than hyperthyroidism and hypothyroidism.

<sup>84</sup> The United States Patent and Trademark Office ("USPTO") reviews applications to determine whether a claimed invention is: (1) is statutory subject matter; (2) is useful; (3) is novel; (4) would not be considered obvious by a hypothetical person of ordinary skill in the field; and (5) is described well enough that those in the field can make and use the invention. *See* 35 U.S.C. § 101. (The first element of the statutory requirements, statutory subject matter, includes any new process, machine, manufacture, or composition of matter, or any new and useful improvement thereof.) *See also* 35 U.S.C. § 112.

<sup>85</sup> JOHN PALFREY, *INTELLECTUAL PROPERTY STRATEGY* 55 (MIT Press 2012).

<sup>86</sup> 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](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.")

<sup>87</sup> In other words, the patent statute promotes technological progress through the monopoly it offers for the creation and disclosure of something new. *See* Stephen Yelderman, *The Value of Accuracy in The Patent System*, 84 U. CHI. L. REV. 1217, 1263, 1670 (2017). (The system Congress created provides a delicate balance. In exchange for monopoly rights, the innovator must provide a description of how to make and use the invention.) *See also* Max Stul Oppenheimer, *Patents 101: Patentable Subject Matter and Separation of Powers*, 15 Vand. J. Ent. & Tech. L. 1, 8 (2012).

<sup>88</sup> Budget and Financial Information (2022), <https://www.uspto.gov/about-us/performance-and-planning/budget-and-financial-information>. The USPTO budget will increase to \$4.25B in 2022 and patent examiners make commonly make between \$100,000 and \$200,000 per year.

<sup>89</sup> In short, a patent awards the exclusive rights to use and profit from an invention to the holder, backed by the Government. *See* Bryce C. Pilz, *Student Intellectual Property Issues on the Entrepreneurial Campus*, 2 MICH. J. PRIVATE EQUITY & VENTURE CAP. L. 1, 16 (2012). *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.)

## A. Treatments

The treatment options available for thyroid disease depend heavily on the nature and extent to which the body produces and regulates thyroid hormone levels.<sup>90</sup> For example, Hypothyroidism is usually treated by replacing the hormone the Thyroid fails to produce with synthetic hormone.<sup>91</sup> By contrast, Hyperthyroidism may be treated by surgically destroying part of the thyroid gland.<sup>92</sup> In all cases, proper treatment for thyroid disease is vital to patient health.<sup>93</sup> Thyroid hormone imbalance can have deleterious and disastrous consequences including extreme anxiety, depression, and fatigue.<sup>94</sup>

Medication options for treating thyroid disease range depending on the clinical diagnosis and individual patient response. For hypothyroidism, physicians often prescribe synthetic thyroxine.<sup>95</sup> Synthetic thyroxine pills contain hormone like the T<sub>4</sub>, which a healthy thyroid makes naturally.<sup>96</sup> In other words, synthetic thyroxine replaces the hormone that the thyroid can no longer make.<sup>97</sup> Oral levothyroxine (LT<sub>4</sub>) is the standard therapy for patients with hypothyroidism.<sup>98</sup> Both brand-name and generic LT<sub>4</sub> tablets are available.<sup>99</sup>

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<sup>90</sup> 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.”)

<sup>91</sup> Hypothyroidism, American Thyroid Association, 12 (2013), [https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism\\_web\\_booklet.pdf](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.”)

<sup>92</sup> U.S. Patent No. 6,740,680 to Danforth, Jr., et al., Pharmaceutical compositions to tetrac and methods of use thereof (May 25, 2004).

<sup>93</sup> 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.”)

<sup>94</sup> 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](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.”)

<sup>95</sup> U.S. Patent No. 6,936,274 to Hanshaw, Jr., et al., Storage stable thyroxine active drug formulations and methods for their production (August 30, 2005).

<sup>96</sup> Hypothyroidism, American Thyroid Association, 12 (2013), [https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism\\_web\\_booklet.pdf](https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf).

<sup>97</sup> Hypothyroidism, American Thyroid Association, 13 (2013), [https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism\\_web\\_booklet.pdf](https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf).

<sup>98</sup> 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.

<sup>99</sup> *See* Appendix D. *See also* Hypothyroidism, American Thyroid Association, 17 (2013), [https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism\\_web\\_booklet.pdf](https://www.thyroid.org/wp-content/uploads/patients/brochures/Hypothyroidism_web_booklet.pdf). (In the United States, thyroxine pills contain only T<sub>4</sub>. However, some researchers speculate whether a combination of T<sub>4</sub> and T<sub>3</sub> might be better for treating patients. While there have been some early studies, the results have not been particularly promising.)

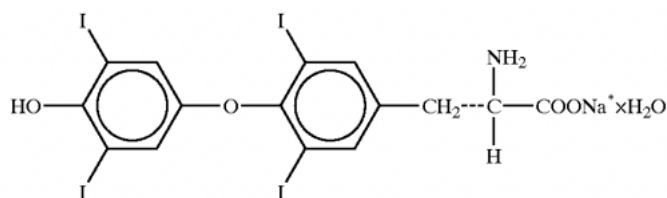


Figure 3<sup>100</sup>

Variations in hyperthyroidism manifestations and corresponding cardiovascular concerns limit treatment options for hypothyroid symptoms.<sup>101</sup> However, drug therapy for hyperthyroidism typically involves antithyroid drugs.<sup>102</sup> Two main antithyroid drugs are propylthiouracil and methimazole, which inhibit organic iodine binding.<sup>103</sup> Additionally, in some cases treatment with glucocorticoids<sup>104</sup> has shown limited effect in treating hyperthyroidism.<sup>105</sup>

Yet, key problems persist. For example, pharmacists often switch between LT<sub>4</sub> formulations which have been determined bioequivalent.<sup>106</sup> However, even small differences between LT<sub>4</sub> formulations can cause significant changes in TSH levels.<sup>107</sup> Changes may cause clinical symptoms, some of which can be caused by inactive ingredients.<sup>108</sup> As such, pharmaceutical swapping is a particular concern in vulnerable populations, including elderly, pregnant, and pediatric patients.<sup>109</sup>

<sup>100</sup> U.S. Patent No. 6,555,581 to Franz, et al., Levothyroxine compositions and methods (April 29, 2003).

<sup>101</sup> 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.”)

<sup>102</sup> 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.)

<sup>103</sup> 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.)

<sup>104</sup> Glucocorticoids are corticosteroids, a class of steroid hormones. Glucocorticoids bind to the glucocorticoid receptor in cells.

<sup>105</sup> U.S. 9,206,154, to Gershengorn, et al., Inverse agonists and neutral antagonists for the TSH receptor (December 8, 2015).

<sup>106</sup> 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 LT<sub>4</sub> formulations based on serum thyroxine (T<sub>4</sub>) 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](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.”)

<sup>107</sup> 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>.

<sup>108</sup> *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<sub>4</sub> preparation if possible. If the LT<sub>4</sub> preparation is changed, TSH levels should be evaluated and, if necessary, the dose of LT<sub>4</sub> adjusted.)

<sup>109</sup> 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>.

An important area for improvement is the development of combination therapy. One problem with current treatment options is they only include T<sub>4</sub>. However, recent research shows that the thyroid produces both T<sub>4</sub> and T<sub>3</sub>.<sup>110</sup> Most of the thyroid hormone production is T<sub>4</sub>, but there is some T<sub>3</sub> produced as well. In fact, treating patients with both T<sub>4</sub> and T<sub>3</sub> at the right ratio would help with treatment effectiveness. For example, T<sub>3</sub> supplementation helps with depression.<sup>111</sup>

## B. Data

Healthcare will be the field having the most impact on humanity's future and as such is also the ripest for breakthrough innovation. This is particularly true for the thyroid, which is often ignored as part of a larger field in endocrinology. The confluence of healthcare and innovation is well presented through the patent system. Any new and useful process or machine is a patentable invention.<sup>112</sup> This Part explores inventions and patents for treatments to thyroid diseases.

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.

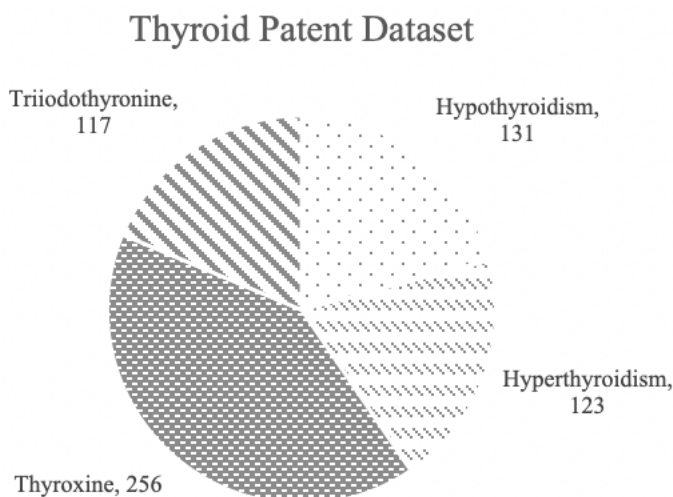


Figure 4<sup>113</sup>

<sup>110</sup> Cristiane Gomes-Lima, Can Reverse T<sub>3</sub> Assay Be Employed to Guide T<sub>4</sub> vs. T<sub>4</sub>/T<sub>3</sub> Therapy in Hypothyroidism?, *Front. Endocrinol., Sec. Thyroid Endocrinology*, (11 December 2019), <https://doi.org/10.3389/fendo.2019.00856>. ("In humans, a normal thyroid gland produces ~85 mcg of T<sub>4</sub> and 6.5 mcg of T<sub>3</sub> daily (1). Thus, the ratio of T<sub>4</sub>:T<sub>3</sub> that is directly secreted from the thyroid gland is around 13:1.")

<sup>111</sup> Kenneth Ain, M.D., and M. Sara Rosenthal, PH.D., *The Complete Thyroid Book*, 262 (2011).

<sup>112</sup> 35 U.S.C. § 101.

<sup>113</sup> 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.)

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<sub>4</sub> (256) and Triiodothyronine T<sub>3</sub> (117) are included in the dataset because they are the effective output for the Thyroid Control Loop.

The goal for the dataset is to provide access to key information relating to treatments for thyroid disease. The dataset was collected from the USPTO database through structured human techniques in compliance with USPTO policy.<sup>114</sup> Importantly, the USPTO severely restricts public access to patent data, which as a policy must end.<sup>115</sup> The initial terms were selected to pinpoint patents for thyroid disease and thyroid hormone by searching the legal claims for key terms. The dataset is currently limited to patents granted between 1999-2019. The Thyroid Dataset is stored in two formats XLS and CSV for processing.

Figure 5 depicts analysis for claims<sup>116</sup> in the Thyroid Patent Dataset. One theory is valuable patents contain more claims than ordinary patents.<sup>117</sup> The intuition behind this reasoning is consistent with the USPTO fee structure.<sup>118</sup> However, there are exceptions to this theory, where patents with fewer claims are more valuable.

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<sup>114</sup> 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](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.”)

<sup>115</sup> *Id.* The USPTO refuses to allow inventors, small business, and researchers access to key patent data necessary to promote technical progress and innovation. Instead, the USPTO claims to make data available to the public through a contract with ReedTech, a Lexis subsidiary. However, the data the USPTO provides is 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.

<sup>116</sup> 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](https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2844964). (Claims represent the legal bounds of the invention.)

<sup>117</sup> John R. Allison, et al. *Valuable Patents*, 92 GEO. L.J. 435, 438 (2004).

<sup>118</sup> 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.)

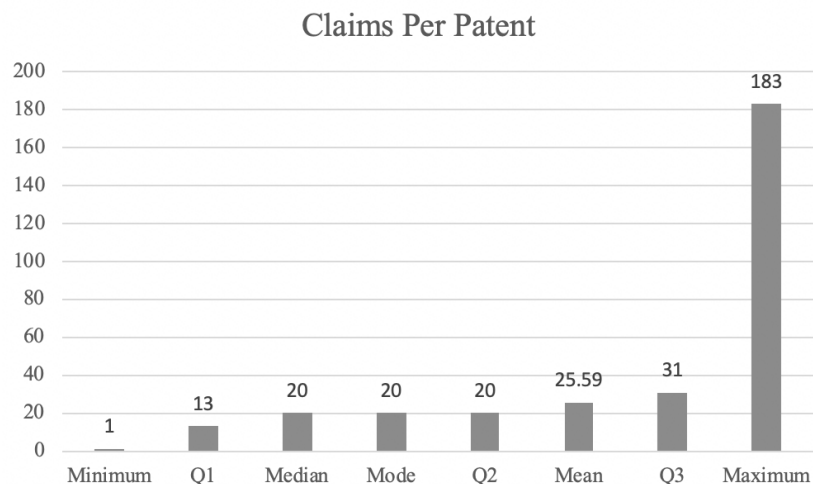


Figure 5<sup>119</sup>

Owned by Ilypsa, Inc., U.S. Patent 8,349,305, *Crosslinked amine polymers*, contained the maximum 183 claims.<sup>120</sup> 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.<sup>121</sup>

A second theory is valuable patents tend to cite more prior art.<sup>122</sup> This reasoning is commensurate with time and money spent on patent search, research, and drafting – each of which positively corresponds with cost. Figure 6 models the prior art citations for the Thyroid Patent Dataset.

<sup>119</sup> 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.)

<sup>120</sup> U.S. Patent 8,349,305 to Cheng, et al., *Crosslinked amine polymers* (January 8, 2013).

<sup>121</sup> 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).

<sup>122</sup> John R. Allison, et al. *Valuable Patents*, 92 GEO. L.J. 435, 438 (2004).



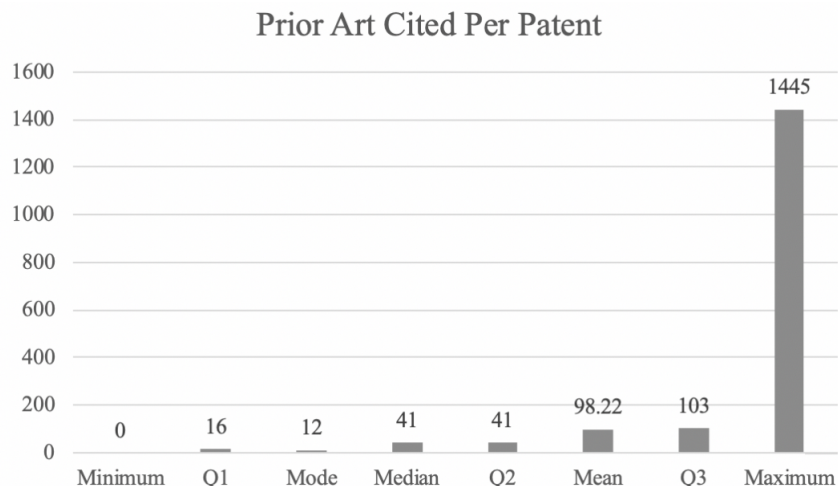


Figure 6<sup>123</sup>

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.<sup>124</sup> 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.<sup>125</sup>

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.<sup>126</sup>

<sup>123</sup> 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.)

<sup>124</sup> U.S. Patent No. 9,039,994 to Van Eyk, et al., *Biomarkers for myocardial ischemia* (May 26, 2015).

<sup>125</sup> 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).

<sup>126</sup> 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 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).

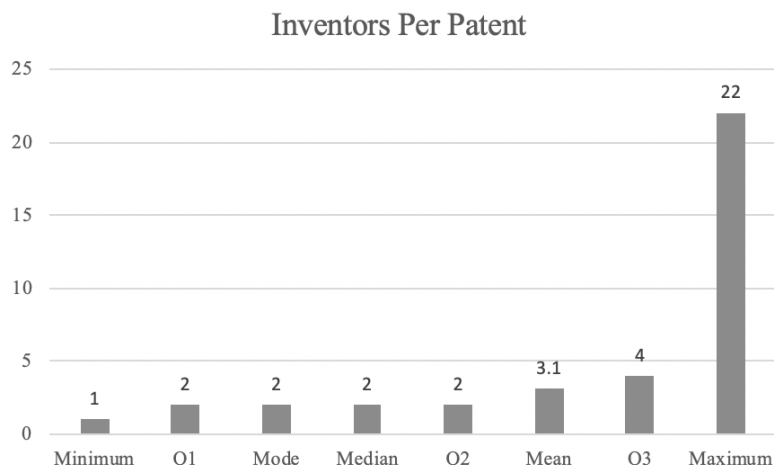


Figure 7<sup>127</sup>

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.<sup>128</sup> 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.<sup>129</sup>

### C. Claims

Claims are the most important part of a patent because they declare the invention<sup>130</sup> because claims are the only part of the patent that can be infringed.<sup>131</sup> The USPTO issues patents for claims it determines satisfy the statutory requirements.<sup>132</sup> Further, a challenge to an issued patent will succeed if the challenger can show that any of the requirements have not been met.<sup>133</sup> 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.<sup>134</sup> Three claim drafting considerations crucial to Thyroid Patents are: nonobviousness, novelty, and scope.

<sup>127</sup> 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.)

<sup>128</sup> 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).

<sup>129</sup> The *ad hominem* fallacy refers to logical arguments relating to a person, rather than the position they are maintaining.

<sup>130</sup> Mark A. Lemley, *The Changing Meaning of Patent Claim Terms*, 104 MICH. L. REV. 101, 101 (2005).

<sup>131</sup> Kevin F. O'Malley, et. al., 3A FED. JURY PRAC. & INSTR. § 158:41 (6th ed. 2019).

<sup>132</sup> Max Stul Oppenheimer, *Patents 101: Patentable Subject Matter and Separation of Powers*, 15 VAND. J. ENT. & TECH. L. 1, 4 (2012).

<sup>133</sup> Max Stul Oppenheimer, *Patents 101: Patentable Subject Matter and Separation of Powers*, 15 VAND. J. ENT. & TECH. L. 1, 4 (2012).

<sup>134</sup> Mark A. Lemley, *The Changing Meaning of Patent Claim Terms*, 104 Mich. L. Rev. 101, 102 (2005).

The nonobviousness doctrine seeks to ensure patents are granted only for technologically significant advances to stimulate useful innovation.<sup>135</sup> 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”.<sup>136</sup> 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.”<sup>137</sup>

The statute requires that obviousness be judged from the perspective of the person having ordinary skill in the art.<sup>138</sup> 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.”<sup>139</sup>

Here, the nonobvious advance composed two elements, suppressing TSH secretion and a pharmaceutical composition including Tetrac<sup>140</sup> and other compounds. Until this patent, the state-of-the-art reflects Levothyroxine<sup>141</sup> was considered the only pharmaceutical composition capable of treating thyroid disease.

Nonobviousness is a question of law,<sup>142</sup> but it relies upon factual inquiries surrounding the differences between the prior art and the application’s claims.<sup>143</sup> The goal for the nonobviousness requirement is to limit patents to only those inventions representing a sufficiently large advance

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<sup>135</sup> 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](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.”)

<sup>136</sup> 35 U.S.C. § 103 (2013).

<sup>137</sup> 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](https://papers.ssrn.com/sol3/papers.cfm?abstract_id=1119723).

<sup>138</sup> *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).

<sup>139</sup> U.S. Patent No. 6,740,680 to Danforth, Jr., et al., *Pharmaceutical compositions to tetrac and methods of use thereof* (May 25, 2004).

<sup>140</sup> 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.

<sup>141</sup> U.S. Patent No. 6,555,581 to Franz, et al., *Levothyroxine compositions and methods* (April 29, 2003).

<sup>142</sup> *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

<sup>143</sup> 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](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.)

over previously known technology.<sup>144</sup> To one skilled-in-the-art, the degree to which an invention advances the art may be entirely subjective.<sup>145</sup> And yet, in addition to nonobvious, patentable claims must also be for something new.

A second component for patent claims is that they must claim a novel invention.<sup>146</sup> In fact, patents are validated technical advancements for new products and innovation services.<sup>147</sup> The law requires that an invention be novel, or new, to be granted a patent.<sup>148</sup> 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.”<sup>149</sup>

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.<sup>150</sup> 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

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<sup>144</sup> *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570 (Fed. Cir. 1996).

<sup>145</sup> 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.”)

<sup>146</sup> 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.”)

<sup>147</sup> 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.”)

<sup>148</sup> 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](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](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.”)

<sup>149</sup> 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.)

<sup>150</sup> 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.”)

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.”<sup>151</sup>

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.<sup>152</sup> 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 patent.”<sup>153</sup> The intuition is that synthesizing divergent ideas is a characteristic for original research.<sup>154</sup>

A patent’s scope depends on the relevant patent’s defined protectable rights.<sup>155</sup> The scope question is not limited to validity or infringement.<sup>156</sup> Rather, it refers to a range of patent rights protecting monopoly.<sup>157</sup> 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

<sup>151</sup> 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.”)

<sup>152</sup> 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.

<sup>153</sup> Elona Marku, et al., Quantity at expense of quality? Measuring the effects of “successful” M&A on innovation performance 8 (2020).

<sup>154</sup> 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.

<sup>155</sup> 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](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.)

<sup>156</sup> 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](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.)

<sup>157</sup> Dan L. Burk & Mark A. Lemley, Policy Levers in Patent Law, 89 VA. L. REV. 1575, 1675 (2003).

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.”<sup>158</sup>

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<sup>159</sup> is the broadest transitional phrase and consisting of<sup>160</sup> 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.”<sup>161</sup>

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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<sup>158</sup> U.S. Patent No. 9,980,933, to Mousa, et al., Thyroid hormone analogs and methods of use (May 29, 2018).

<sup>159</sup> *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.)

<sup>160</sup> *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.)

<sup>161</sup> 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.<sup>162</sup>

Some suggest, patent law has gaps resulting from conceptual separations in patentability, infringement, and defenses.<sup>163</sup> For example, a party may successfully argue a patent claim means one thing in one context, but something totally different in another.<sup>164</sup> 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.<sup>165</sup> Ultimately, scope is a term of art and is best understood as a continuous scale.<sup>166</sup> In other words, whether a claim is broad or narrow is a subjective ascription, often based on relative comparison.<sup>167</sup> As such, data is a critical advantage for the modern firm because data defines the targets to which the claim is compared.

### III. Clinical Commercialization

The hardest part of inventing new treatments or biotechnologies is commercialization. Commercialization is the process of bringing new drugs and biotechnologies to market. The Commercialization process can take over ten years in certain circumstances and in fact there are even publicly traded pharmaceutical companies without revenue that have completely failed to commercialize their innovations over the course of a decade. However, given the appropriate strategy, commercialization may happen faster. Yet, it is a difficult balance between customer safety and meeting need in the market.

#### A. Value

Probably the most important part of the commercialization process is adding value. The best way to add value is to invent solutions to problems. For example, in the context of thyroid disease there exists a need for value to be added through solutions to both general and narrow forms of thyroid disease. More often, in the context of patent law, value for innovations is calculated when infringement occurs in the context of damages.<sup>168</sup>

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<sup>162</sup> 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](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.”)

<sup>163</sup> 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.)

<sup>164</sup> Mark A. Lemley & Mark P. McKenna, Scope, 57 WM. & MARY L. REV 2197, 2220-2221 (2015).

<sup>165</sup> 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).

<sup>166</sup> 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](https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3554925).

<sup>167</sup> 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](https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3527154).

<sup>168</sup> 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](https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3099060).

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.”<sup>169</sup> 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.<sup>170</sup> Direct infringement is the broadest clause conferring infringement liability in the Patent Act.<sup>171</sup> 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.<sup>172</sup> If a patent is found to be valid and infringed, its owner is entitled to infringement damages.<sup>173</sup>

Courts have interpreted the Patent Act to mean that patent damages come in two primary measures: lost profits and reasonable royalties.<sup>174</sup> Lost profits provide the patentee with the profits the patentee would have made but for the infringing sales as damages in litigation.<sup>175</sup> Proving lost profits, however, is not an easy endeavor.<sup>176</sup> 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.<sup>177</sup>

The second measure for damages is reasonable royalties, which are the dominant damages determination.<sup>178</sup> Today, over 80% of all patent damage awards are reasonable royalties.<sup>179</sup> As such, some describe the Reasonable Royalty Model<sup>180</sup> as a historic bedrock technique in patent license valuation.<sup>181</sup> Courts typically apply a fifteen factor analysis set out in *Georgia-Pacific*

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<sup>169</sup> 35 U.S.C. § 284 (2015).

<sup>170</sup> 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.)

<sup>171</sup> 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.”)

<sup>172</sup> 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](https://robots.law.miami.edu/2019/wp-content/uploads/2019/03/Ebrahim_Patent-Infringement.pdf).)

<sup>173</sup> 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](https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3099060).

<sup>174</sup> 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](https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3099060).

<sup>175</sup> 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](https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3099060).

<sup>176</sup> 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](https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3099060).

<sup>177</sup> *Panduit Corp. v. Stahl Bros. Fibre Works*, 575 F.2d 1152, 1156 (6th Cir. 1978).

<sup>178</sup> 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](https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3099060). (Arguing tax-related transfer prices are useful evidence for calculating reasonable royalty patent damages.)

<sup>179</sup> 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](https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3099060).

<sup>180</sup> 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.”)

<sup>181</sup> 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.)



*Corp. v. United States Plywood Corp* to determine reasonable royalty.<sup>182</sup> As such, judicial discretion determines questions relating to conflicting evidence for amount.<sup>183</sup> And, courts inevitably have broad judgment in evaluating the relevant patent value factors.<sup>184</sup>

But there are much better ways to value inventions for new treatments for thyroid disease than damages. A better way to think about calculating value is with options pricing<sup>185</sup> because option valuations reflect a more diverse and accurate economic information source.<sup>186</sup> Real options theory can be used to value inventions for thyroid disease to account the value patents add absent infringement, such as security value on corporate balance sheets, as an intellectual asset to attract grant funding and research revenue, or as product for the public good and the associated tax benefits.<sup>187</sup>

Biotechnology patents are options. For example, the option to choose between exclusively commercializing the patented invention or foregoing commercialization altogether adds value to a company insofar as it provides the ability to shape innovation in the market.<sup>188</sup> One of the first steps in framing patents as real options is to define the patent's market price.<sup>189</sup> The patent's filing fees, and development costs contribute components for the patent option price.<sup>190</sup>

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<sup>182</sup> *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.”)

<sup>183</sup> *General Motors Corp. v. Dailey*, 93 F.2d 938, 942 (6th Cir. 1937).

<sup>184</sup> *Georgia-Pacific Corp. v. United States Plywood Corp.*, 318 F. Supp. 1116, 1120 (S.D.N.Y. 1970).

<sup>185</sup> 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>.

<sup>186</sup> Christopher A. Cotropia, Describing Patents as Real Options, 34 J. Corp. L. 1127, 1128 (2009).

<sup>187</sup> Christopher A. Cotropia, Describing Patents as Real Options, 34 J. Corp. L. 1127, 1131 (2009).

<sup>188</sup> 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.)

<sup>189</sup> 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).

<sup>190</sup> 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.)

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,<sup>191</sup> profits,<sup>192</sup> and royalties.<sup>193</sup> For example, the option price in a licensing contract for a new treatment 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.<sup>194</sup>

Patent valuation methods are a starting point towards better IP strategy.<sup>195</sup> This Paper 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 correlating with patent value with an expert system provides a solution formalizing the decision process. Moreover, the value of new thyroid inventions, and their associate patents are largely tied to the progress through clinical trials made by the inventor.

## B. FDA Trials

Clinical trials are prospective, organized, systematic exposures of patients to an intervention of some kind.<sup>196</sup> Despite widespread fraud and corruption, the U.S. Food and Drug Administration has evolved as one of the world's institutional authorities for conducting and evaluating controlled clinical drug trials.<sup>197</sup> Significant statutory barriers stifle the process by which new drugs and biotechnologies migrate to market. As a result, the public loses out on medical advancements and inventions, which would otherwise save lives and improve the public quality of life.

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<sup>191</sup> Christopher A. Cotropia, *Describing Patents as Real Options*, 34 J. Corp. L. 1127, 1135 (2009).

<sup>192</sup> Maria Isabella Leone, *The Option Value of Patent Licenses*, 5 (2007), [https://www.researchgate.net/publication/252398618\\_The\\_option\\_value\\_of\\_patent\\_licenses](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.)

<sup>193</sup> 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.)

<sup>194</sup> Maria Isabella Leone, *The Option Value of Patent Licenses*, 5 (2007), [https://www.researchgate.net/publication/252398618\\_The\\_option\\_value\\_of\\_patent\\_licenses](https://www.researchgate.net/publication/252398618_The_option_value_of_patent_licenses).

<sup>195</sup> 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](https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3410086).

<sup>196</sup> Suzanne White Junod, Ph.D., *FDA and Clinical Drug Trials: A Short History*, 1 (2008), <https://www.fda.gov/media/110437/download>. (Based largely on observations and tested through time by trial and error, ancient medicine such as that practiced by the Egyptians, Babylonians, and Hebrews was closely allied with religion.)

<sup>197</sup> Suzanne White Junod, Ph.D., *FDA and Clinical Drug Trials: A Short History*, 1 (2008), <https://www.fda.gov/media/110437/download>.

The FDA plays an essential role in the process by which new drugs and biotechnologies come to market.<sup>198</sup> However, more essential is that the public and private interests are aligned through a transparent, lucid, and accessible incentive structure embedded in the regulatory climate. There are many interests at play in designing incentives to promote and foster innovation and progress.<sup>199</sup> As such, structuring incentives for firms, the public, and the FDA is crucial to creating an optimal regulatory framework.

To bring any new drug or device relating to the human thyroid to market you need to get FDA clearance. And the FDA approval path depends on the risk of the device. In some circumstances, a device may be able to be fast tracked to approval if there is a predicate device. For the predicate device to be successful, the device needs to be very similar. There will be a comparison of both mechanics and disease for which the device is manufactured. Devices are regulated by algorithm and there is guidance around software as a medical device. Another issue that may arrive relates to software as a medical device.<sup>200</sup>

For purposes of FDA trials there are three categories of medical devices.<sup>201</sup> The first category is Category 1 which requires full clinical trials and poses the most severe risk to life. The second category is Category 2 which includes an accelerated approval path and has milder risk and lacks any potentially lethal risk. The third category is Category 3, where devices carry the least risk and require no clinical trials for approval. Still there may be better opportunities for innovation outside the United States where there exists great opportunity to solve real problems relating to thyroid disease.

### C. Innovation

There is opportunity for innovation relating to thyroid disease. In fact, treatments for thyroid disease have not improved in over five decades since screening for hypothyroidism using antibodies was originally first introduced.<sup>202</sup> Inventing is the only way to innovate; it's a process by which problems are solved anew.

Inventions are new and useful machines or processes.<sup>203</sup> Inventing new drugs and biotechnologies for solving problems and curing conditions relating to thyroid disease is easy. The hard part, bringing inventions to life, is an extremely long, meticulous, and daunting challenge.

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<sup>198</sup> Patricia J. Zettler, et al., *Implementing a Public Health Perspective in FDA Drug Regulation*, 73 Food and Drug Law Journal, 221, 222 (2018). ("FDA, through its authority over the drug market, undoubtedly has an important role to play in this landscape.") See also Suzanne White Junod, Ph.D., *FDA and Clinical Drug Trials: A Short History*, 1 (2008). ("The FDA is a prominent institutional authority for conducting and evaluating clinical drug trials.")

<sup>199</sup> Elizabeth Weeks Leonard, Right to Experimental Treatment: FDA New Drug Approval, Constitutional Rights, and the Public's Health, 37 J. of Law, Medicine and Ethics 6 (2009).

<sup>200</sup> Software as a Medical Device (SaMD) (12/04/2018),

<https://www.fda.gov/medical-devices/digital-health-center-excellence/software-medical-device-samd>.

<sup>201</sup> U.S. Food & Drug Administration, How to Find and Effectively Use Predicate Devices (09/04/2018),

<https://www.fda.gov/medical-devices/premarket-notification-510k/how-find-and-effectively-use-predicate-devices>.

<sup>202</sup> Elizabeth A. McAninch, MD and Antonio C. Bianco, MD, PhD, The History and Future of Treatment of Hypothyroidism, Ann Intern Med. 2016 January 5; 164(1): 50–56. doi:10.7326/M15-1799.

<sup>203</sup> 35 U.S.C. § 101.

So, it's important to study history to move forward. Generally, inventions are as good as the history they erase. For inventions relating to thyroid disease, it's possible to overwrite roughly fifty years of history because treatments have not changed much since.<sup>204</sup> According to Dr. Elizabeth McAninch, the world's leading expert on thyroid disease and a current Professor at Stanford Medical School, "Two major developments in the 1970s led to a transition in clinical practice: 1) The development of the serum TSH radioimmunoassay led to the discovery that many patients were overtreated, resulting in a dramatic reduction in thyroid hormone replacement dosage, and 2) the identification of peripheral deiodinase-mediated T4-to-T3 conversion provided a physiologic means to justify L-thyroxine monotherapy."<sup>205</sup>

An important evolution for the future of thyroid hormone treatment will likely be the use of combination therapy. Indeed, providing new mechanisms for the treatment of thyroid that more closely model the biological synthesis of thyroid hormone offer the opportunity for improved treatment options and maintaining patient metabolic homeostasis.<sup>206</sup> Still patients are only treated with LT4. But a common problem with symptom-based diagnostics is that there is no method for identifying the root cause of symptoms and therefore, it is likely that many peripheral problems relating to unstable metabolic control stemming from thyroid disease go unnoticed.

The secret to inventing any new cure or treatment has three steps. First, write down the problem. Second, study and think about the problem. Third, write down the solution in patentable form. Thus, the process for inventing new treatments for thyroid disease is relatively straightforward, insofar as the process simply requires the identification of existing problems, which are abundant, and the focus to generate a solution. However, large institutional barriers still loom to slow innovation and progress more generally.

## Conclusion

This Paper proceeds in three parts. Part I explored thyroid disease, including diagnostics, hypothyroidism, and hyperthyroidism. Part II empirically investigated inventions for treatments to thyroid disease through the lens of the patent system. Part III consolidated considerations for commercialization of inventions for treating thyroid disease. As evolution<sup>207</sup> continues, the future will likely be defined by human-machine symbiosis. In turn, the process of integration with the next generation of humans will likely lead to a complete cure for human thyroid disease, it's only a matter of time. In the words of Jonas Salk, "There is hope in dreams, imagination, and in the courage of those who wish to make those dreams a reality."

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<sup>204</sup> Elizabeth A. McAninch, MD and Antonio C. Bianco, MD, PhD, The History and Future of Treatment of Hypothyroidism, *Ann Intern Med.* 2016 January 5; 164(1): 50–56. doi:10.7326/M15-1799.

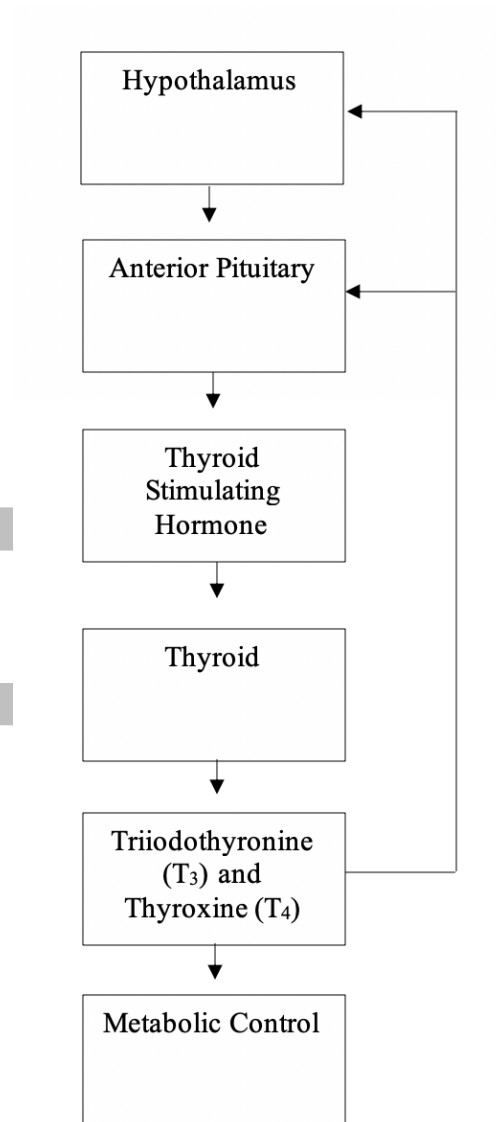
<sup>205</sup> Elizabeth A. McAninch, MD and Antonio C. Bianco, MD, PhD, The History and Future of Treatment of Hypothyroidism, *Ann Intern Med.* 2016 January 5; 164(1): 50–56. doi:10.7326/M15-1799.

<sup>206</sup> Cristiane Gomes-Lima, Can Reverse T3 Assay Be Employed to Guide T4 vs. T4/T3 Therapy in Hypothyroidism?, *Front. Endocrinol., Sec. Thyroid Endocrinology*, (11 December 2019), <https://doi.org/10.3389/fendo.2019.00856>.

<sup>207</sup> Charles Darwin, *On The Origin of Species by Means of Natural Selection, or The Preservation of Favored Races in The Struggle for Life* 14 (1859). (When we look to the individuals of the same variety of our ancestors, one of the most striking points is they generally differ much more from each other, than do the individuals of any one species or variety in a state of nature.)

## 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 <sub>3</sub> and Thyroxine T <sub>4</sub> .
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 <sub>3</sub>	A thyroid hormone.
Thyroxine T <sub>4</sub>	A thyroid hormone.
Metabolic Control	Metabolism refers to the chemical reactions necessary for life, the control of which results from endocrine processes.

## Appendix C. 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

## Appendix D. Symptoms for Thyroid Disease

<b>Hypothyroidism<sup>208</sup></b>	<b>Hyperthyroidism<sup>209</sup></b>
<ol style="list-style-type: none"> <li>1. Weight gain.</li> <li>2. Depression.</li> <li>3. Slow movements and thoughts.</li> <li>4. Muscle aches and weakness.</li> <li>5. Muscle cramps.</li> <li>6. Dry and scaly skin.</li> <li>7. Brittle hair and nails.</li> <li>8. Loss of libido.</li> <li>9. Pain, numbness, and a tingling sensation.</li> <li>10. Tiredness.</li> <li>11. More sensitivity to cold.</li> <li>12. Constipation.</li> <li>13. Dry skin.</li> <li>14. Puffy face.</li> <li>15. Hoarse voice.</li> <li>16. Coarse hair and skin.</li> <li>17. Muscle weakness.</li> <li>18. Muscle aches, tenderness, and stiffness.</li> <li>19. Unusually heavy menstrual cycles.</li> <li>20. Thinning hair.</li> <li>21. Slowed heart rate, also called bradycardia.</li> <li>22. Depression.</li> <li>23. Memory problems.</li> <li>24. Feeding problems.</li> <li>25. Poor growth.</li> <li>26. Poor weight gain.</li> <li>27. Jaundice.</li> <li>28. Constipation.</li> <li>29. Poor muscle tone.</li> <li>30. Dry skin.</li> <li>31. Hoarse crying.</li> <li>32. Enlarged tongue.</li> <li>33. Umbilical hernia.</li> <li>34. Poor growth that leads to short stature.</li> <li>35. Delayed development of permanent teeth.</li> <li>36. Delayed puberty.</li> <li>37. Poor mental development.</li> </ol>	<ol style="list-style-type: none"> <li>1. Losing weight without trying.</li> <li>2. Tachycardia.</li> <li>3. Arrhythmia.</li> <li>4. Pounding of the heart, sometimes called heart palpitations.</li> <li>5. Increased hunger.</li> <li>6. Nervousness, anxiety, and irritability.</li> <li>7. Tremor.</li> <li>8. Sweating.</li> <li>9. Changes in menstrual cycles.</li> <li>10. Increased sensitivity to heat.</li> <li>11. Changes in bowel patterns.</li> <li>12. Swelling at the base of the neck.</li> <li>13. Tiredness.</li> <li>14. Muscle weakness.</li> <li>15. Sleep problems.</li> <li>16. Warm, moist skin.</li> <li>17. Thinning skin.</li> <li>18. Fine, brittle hair.</li> <li>19. Nervousness, anxiety, and irritability.</li> <li>20. Hyperactivity.</li> <li>21. Mood swings</li> <li>22. Difficulty sleeping</li> <li>23. Feeling tired all the time</li> <li>24. Sensitivity to heat.</li> <li>25. Muscle weakness</li> <li>26. Diarrhea.</li> <li>27. Needing to pee more than usual.</li> <li>28. Persistent thirst.</li> <li>29. Itchiness.</li> <li>30. Loss of interest in sex.</li> </ol>

<sup>208</sup> NHS, Symptoms-Underactive thyroid (hypothyroidism) (2022), <https://www.nhs.uk/conditions/underactive-thyroid-hypothyroidism/symptoms/>. See also Mayo Clinic, Hypothyroidism (underactive thyroid) (2022), <https://www.mayoclinic.org/diseases-conditions/hypothyroidism/symptoms-causes/syc-20350284>.

<sup>209</sup> May Clinic, Hyperthyroidism (overactive thyroid) (2022). See also Symptoms-Overactive thyroid (hyperthyroidism) (2022), <https://www.nhs.uk/conditions/overactive-thyroid-hyperthyroidism/symptoms/>.