# A disease mapping for Elithia

## Diagnostic and therapeutic gaps in neurobiological and immunological conditions

**Internship report** – Master's in Science and Business Management

**Student**: Asier Segura Elorza (student number: 7017014)

**Supervisors**: Jordy Breuker and Hein Roelfsema

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**Abstract:**

There are plenty of medical conditions, each of them with its own unmet medical needs. NLC is a health-tech venture builder that aims to tackle these unmet medical needs by building startups. NLC builds startups through entrepreneurship at scale, i.e., seizing all the knowledge gathered in developing these ventures and standardizing the process of building them up so that it happens faster and more efficiently. NLC provides funding to its ventures through its funds. The newest fund, Elithia, is focused on bringing the next generation of impactful biotech ventures in the fields of neurobiology and immunology. However, the unmet medical needs of these conditions remain unknown to the Elithia team. In consequence, in this thesis report, I have reviewed 39 neurobiological and immunological conditions and shed light on the current diagnostic and therapeutic gaps. To this end, I have collected the data in fact sheets – this way, the data, and findings are more accessible to the Elithia team. Following this review, I could observe the high variability regarding unmet medical needs between all these conditions. Yet, the diagnostic needs have stood out. Molecular or digital biomarkers would be of much help in diagnosing a wide array of conditions such as bipolar disorder or systemic lupus erythematosus and help the patient receive adequate treatment early on.

**Abbreviations:**

AD: Alzheimer's disease

ADHD: Attention-deficit hyperactivity disorder

AEDs: Anti-epileptic drugs

AN: Anorexia nervosa

APA: American Psychiatry Association

ASD: Autism spectrum disorder

BED: Binge-eating disorder

BN: Bulimia nervosa

CBT: Cognitive behavioral therapy

CeD: Celiac disease

CFS: Cerebrospinal fluid

CNS: central nervous system

CrD: Crohn's disease

CSA: Central sleep apnea

DALY: Disability-adjusted life-year

DLD: Developmental learning disorder

DMT: Disease-modifying therapy

DSM: Diagnostic and statistical manual of mental disorders

EMA: European Medicine Agency

ET: Essential tremor

FDA: US Food and Drug Agency

GAD: Generalised anxiety disorder

GD: GlobalData

IBD: Inflammatory bowel disease

ICD: International classification of diseases

IDD: Intellectual disability disorder

NDD: Neurodevelopmental disorder

NHS: UK National Health Service

NIH: National Institutes of Health

NSAIDs: Non-steroidal anti-inflammatory drugs

OCD: Obsessive-compulsive disorder

OSA: Obstructive sleep apnea

PD: Parkinson's disease

PNS: Peripheral nervous system

RA: Rheumatoid arthritis

SLE: Systemic lupus erythematosus

SWD: Sleep-wake disorder

TRD: Treatment-resistant depression

TS: Tourette syndrome

UC: Ulcerative colitis

WHO: World Health Organisation

# 1. Introduction

## 1.1. NLC (and a brief personal note)

When I applied back in December for a company called NLC I had little idea what it was about. I could read in the LinkedIn profile or on the website that it was a "venture builder". I would read about the company and this quite rare business model, but my lack of understanding would remain quite intact. And when I started later in March, it took me a couple of months to understand what it was all about. But in the end, I have understood that at the core of NLC we can find people who desire to make an impact in healthcare and the concept of "entrepreneurship at scale". This consists in seizing all the knowledge gathered in developing these ventures and standardizing the process of building them up so that it happens faster.

NLC was founded in 2015 based on the realization that most clinical technologies do not reach the patient while bringing them to the market will be life-changing for many. As such, NLC's mission is to advance in health and make it accessible for everyone. Entrepreneurship is essential to get a venture through the early stages, where you really need to put in the hard graft and work on many levels at the same time. To achieve it, NLC makes use of an extensive network: inventors and research institutes that want to bring their inventions to the market with NLC; medical, technical, and business specialists that will help evaluate the inventions; investors that are willing to take the risk and invest in early seed start-ups and entrepreneurs and advisors that help NLC grow the ventures.

In addition, NLC operates at the beginning of the risk curve (**Figure 1**) where the risk is high, and the invested capital is low. This creates an opportunity to make an impact by utilizing the previously mentioned entrepreneurship at scale to lower the risk curve of NLC's individual ventures, to de-risk these ventures faster at low(er) cost, and to scale NLC's portfolio to further (statistically) de-risk the company's model.
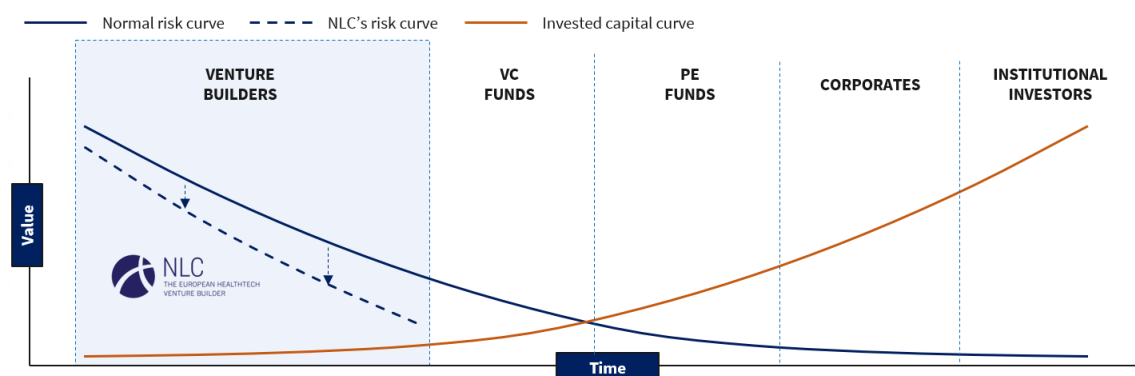


**Figure 1.** Normal risk curve and NLC's impact on it (NLC.health).

## 1.2.    Elithia

NLC has set up several investment funds to provide investors access to a diversified portfolio of impactful healthtech ventures with one single investment, allowing them to spread their risk over multiple investments at low transaction costs. The first fund founded was Momentum, in early 2020. Later that year, the Stepping Stone fund was set up.

Elithia, named after the Greek goddess of birth, is the third and most recent NLC fund and it aims to translate breakthrough science into the next generation of impactful biotech ventures.

Elithia focuses on conditions of the central nervous system (CNS) and immune systems, in addition to the middle ground – neuroimmune conditions. These three areas have extremely high unmet medical needs and recently, there have been several scientific breakthroughs that have allowed us a better understanding of the mechanisms of these specific diseases. In addition, these fields are relatively less competitive and capital intensive than fields like oncology and cardiology.

## 1.3.    Diseases and classifications

As said, through Elithia, NLC aims to found ventures to meet unmet needs regarding diseases of the CNS and the immune system. However, what is a disease?

This question may seem simple at first glance. According to Merriam-Webster, a disease is "a condition of the living animal or plant body or of one of its parts that impairs normal functioning and is typically manifested by distinguishing signs and symptoms". Similarly, Encyclopaedia Britannica defines it as "any harmful deviation from the normal structural or functional state of an organism, generally associated with certain signs and symptoms and differing in nature from physical injury". In consequence, we can observe that diseases are normally associated with measurable and identifiable symptoms in a given time frame, hence, putting in a rather strange situation certain disorders and the vast majority of syndromes. Therefore, I believe the term "medical condition" may be seen as more appropriate from a scientific point of view.

There are plenty of conditions. Even the most proficient of all physicians would fail to mention every one of them. As such, classifying medical conditions according to the biological systems, structures, or organs affected or according to the mechanism, is a necessary endeavor. Among the many classifications available out there, the International Classification of Diseases (ICD), a health statistics coding tool published by the World Health Organisation (WHO), might well be the most prominent (ed. Lancet, 2019).  The ICD is reviewed periodically – the latest version is the 11th version of the ICD (ICD-11) published in 2019. (ed. Lancet 2019). Still, in the field of mental health, the diagnostic and statistical manual of mental disorders (DSM) is also worth mentioning.

However, it is relevant to address that these classifications are designed for a better diagnosis of medical conditions, they are not scientifically validated tools - they are used for medical and statistical purposes exclusively (Allsopp et al., 2019; Kurbasic et al., 2008).

## 1.4.    The central nervous system

The nervous system is a complex network that enables an organism to interact with its surroundings (Ludwig et al., 2021) and it is subdivided into the CNS and the peripheral nervous system (PNS). The CNS is the brain and spinal cord, while the PNS consists of everything else. The CNS' responsibilities include receiving, processing, and responding to sensory information (Thau et al., 2022).

As such, we can define the conditions of the CNS as those related to the brain and the spinal cord. Based on the ICD-11, I have classified CNS conditions into the following groups:

1.  Psychiatric conditions: it refers to mental, behavioral, and neurodevelopmental conditions. These are characterized by clinically significant disturbance in an individual's cognition, emotional regulation, or behavior that reflects a dysfunction in the psychological, biological, or developmental processes that underlie mental and behavioral functioning. For example, depression, schizophrenia, or ADHD.

2.  Sleep-wake disorders (SWDs): SWDs are a group of conditions that disturb normal sleep patterns. Inadequate or non-restorative sleep can interfere with normal physical, mental, social, and emotional functioning. Sleep disorders can affect overall health, safety, and quality of life (Karna et al., 2022). For example, chronic insomnia and rem sleep behavior disorder.

3.  Neurological conditions: neurologic conditions affect the physiology of the CNS and PNS. In other words, the brain, spinal cord, cranial nerves, peripheral nerves, nerve roots, autonomic nervous system, neuromuscular junction, and muscles. (WHO, 2016) For example, Alzheimer's disease (AD) and Parkinson's disease (PD).

While CNS conditions can be very different from one another, differing enormously in symptomatology, prevalence/incidence, or ease to diagnose, the impact cannot be negated (Hewer, 1997; Saarni et al., 2007).

Due to this impact, there is a big ongoing effort in understanding the science behind these conditions and developing new therapeutic tools. However, the development of new therapies in neuroscience presents several challenges. The biology and pathophysiology of these conditions tend to be complicated, an issue that is further complicated by the lack of proper translational models, hampering greatly the development of new therapies.

Currently, rodents are the most widely used translational models, however, they present unique challenges that prevent successfully translating the results to humans.

In fact, there is a high rate of failure in the earlier clinical stages. In addition, pharmaceutical corporations often lack the resources (either economic or expertise-related) to undertake the research and scientific understanding of the biological phenomena surrounding these conditions.

## 1.5. The immune system

The immune system has a vital role: it protects your body from harmful substances, germs, and cell changes that could make you ill. It is made up of various organs, cells, and proteins. This system can be activated by antigens. These are proteins that are present on the surfaces of bacteria, fungi, and viruses. When these antigens attach to special receptors in the immune system, a whole series of processes are triggered in the body (InformedHealth.org, 2006).

However, sometimes the immune system fails, either by an excessive reaction or by the lack of it. This leads to a large variety of conditions with potentially fatal impacts on human health. Hence, just like in the case of CNS conditions, there are big ongoing efforts to develop therapeutic tools.

These medical conditions related to the immune system can be broadly classified into the following four groups (Nicholson, 2016):

1. Immunodeficiency: when your immune system fails to respond to an infection.

2. Autoinflammation: when there is an abnormally increased inflammation, due to a dysregulation of inflammatory cytokines in the innate immune system.

3. Autoimmunity: when the adaptative immune system mounts an attack against healthy tissue.

4. Allergy: when an antigen, normally an innocuous environmental protein, triggers an inappropriate immune response.

However, as addressed by El-Shebini et al. (2021), despite the differences in etiology and phenotypic variations, autoinflammatory and autoimmune conditions have common genetic associations, treatment responses, and clinical presentations, consequently, it can be considered as only one group of diseases with a large immune pathological and clinical spectrum. Hence, from here on, I shall use the "autoimmune" term exclusively.

Nonetheless, curing any of these conditions poses real challenges. Unlike cancer, in which eliminating the cancerous cells is the goal, the immune system is necessary – we cannot simply eliminate it. In general, current immune-modulatory drugs used in the treatment of autoimmune diseases are broadly acting, non-disease specific, and, consequently, associated with side effects such as infection and malignant disease. For further information, I recommend reading the review by Fugger et al. (2020).

Similarly, there are no cures for allergic diseases. The main line of dealing with allergies consists in avoiding contact with the allergen that triggers the allergic response. In some instances, it can be certainly difficult, such as hay fever. In these cases, allergen-specific immunotherapy is an effective treatment, particularly, for allergic rhinitis/conjunctivitis,

allergic asthma, and stinging insect hypersensitivity that provides (Moote et al., 2018). Normally it is provided through subcutaneous injections, although the effect wears off after 3-5 years (aaaai.com)

## 1.6.     Neuroimmune diseases

The term "neuroimmunology" is rather new. It was first used on PubMed in 1982 coinciding with the first neuroimmunology congress in Italy and following the launch of the journal of neuroimmunology. This has been mostly because it has been generally regarded as autonomous and the brain protected by the blood-brain barrier (Nutma et al., 2019). However, neuroimmunology is a rapidly evolving field with significant diagnostic and treatment advancements over the last decade (Piquet and Álvarez, 202).

The immune activation against neuronal antigens forms the basis of almost all neuroimmune diseases. They are characterized mainly by inflammatory autoimmune (cell-mediated or humoral), demyelinating, neurodegenerative, parainfectious, paraneoplastic, and traumatized neurological deficit. In these diseases, neuroinflammation is prominent. Several studies have suggested a strong link between neuroinflammation and neurodegenerative diseases. Further, CNS inflammation has also been reported in patients with depression, bipolar disorder, or schizophrenia (Ransohoff et al. 2015). However, evidence addressing the involvement of neuroinflammation in the neurodegenerative and neuropsychiatric processes is still lacking.

Interestingly, conventional immunotherapeutic interventions, corticosteroids, and immunosuppressors provide a variable amount of clinical benefits in several neuroimmune disorders (Hughes et al., 2017). Furthermore, the precise targeting of the specific inflammatory pathways and immune cell activation and infiltration in the nervous system has been shown a promise to control the clinical course (Lorscheider et al., 2018; Faissner and Gold, 2010). In any case, current therapies aim to modulate neuroinflammation arising during these conditions and future approaches should aim at disease prevention (Fugger et al. 2020)

In short, the immune system and the CNS are not separate, unrelated systems.

## 2. Aims

This thesis report is a disease mapping of the CNS and immune system, encompassing conditions that could be classified as neurobiological, immunological, and neuroimmunological.

The mapping of disease incidence and prevalence has long been a part of public health, epidemiology, and the study of disease in human populations (Koch, 2005), yet incidence and prevalence are not the only two features to be mapped in the present report – diagnostic needs, therapeutic needs, the burden of the disease and trends in academia are also considered.

Yet, the mapping itself is not the ultimate purpose of this project. Here, based on this mapping, I aim to shed light on the current diagnostic and therapeutic gaps in neurobiological and immunological conditions. To this aim, two different perspectives are considered: the unmet medical need present in these conditions and the financial promise a potentially new treatment could offer. This way, this thesis report can be used by NLC and, in particular, the Elithia team to select the most interesting conditions for which new ventures can be built through the Elithia fund.

# 3. Methodology

I mostly based the list of conditions related ot the immune system and CNS on the ICD-11 (ed. Lancet 2019) although other sources were also employed. For instance, for psychiatric conditions, the DSM-v (American Psychiatric Association, 2013) was also employed.

As agreed with Milad Tanazi – lead for Elithia – the orphan or rare diseases were excluded. To make a greater initial impact, we decided to focus this report on the most prevalent conditions. The definition was drawn from the website of the European Medicine Agency (EMA). It defines rare diseases as those with a prevalence lower than 1 in 2000 cases (EMA, 2018). Further, due to the small amount of available literature, I also excluded several conditions.

To gather the data in the most organized way possible, I designed fact sheets, on which my discussion is based. These fact sheets can be found in the annexes and contain the following entries:

1. Name of the condition

2. Category: the category to which the condition belongs. Neurobiological, immunological or neuroimmune disease. If neurobiological – further classification into psychiatric, SWD or neurologic. If immunological, further classification into allergy or autoimmune.

3. Description: a brief overview of the condition.

4. Epidemiology: the prevalence and/or incidence of the condition.

5. Diagnostic needs: according to the information gathered it will be classified on a scale of 1 to 4. It will address the effectiveness of the diagnostic tools, the timeliness, the ease to perform the diagnostic tests, the availability and potential misdiagnosis.

    1. The condition is easily diagnosed based on the symptoms or in a non-invasive manner, and it is very rarely misdiagnosed. Most cases do not go unchecked.

    2. The condition is easily diagnosed, but it is not a straightforward process. Sometimes the patient might need to be monitored and/or costly and somewhat invasive techniques (e.g. Endoscopy) might be needed. The condition is rarely misdiagnosed, although some patients might not go to the doctor and cases might go unchecked.

    3. The condition can be diagnosed, however, it can be an arduous process. Invasive techniques might be needed, e.g., biopsies, and several tests might need to be run to rule out other conditions. Occasionally, the condition might be misdiagnosed or not diagnosed at all.

    4. The diagnosis of the condition is difficult, and oftentimes it is misdiagnosed or not diagnosed at all. It tends to be a ruling-out process in which several

other conditions need to be ruled out before reaching a final diagnosis. Oftentimes, it can be too late to effectively treat the patient.

6. Burden of the dsiease: burden the condition causes on the patients. DALY or disability-adjusted life year is used as a proxy – it is a measure often used to prioritize funds in the public health field and combines indicators – mortality, morbidity and the severity of health conditions – in one measure and represent the health loss or gap to perfect health in a population (hilderink et al. 2020). Nonetheless, in several instances, DALY values were not available. Also, a brief explanation of the burden the condition causes is provided.

7. Treatment needs: current trends in therapies (both pharmacological and non-pharmacological) that are used to treat each condition. Current FDA approved drugs are also mentioned. According to the information gathered I will classify the trends in treatment on a scale of 1 to 4.

    1. There are effective treatments available with low side effects that can cure or minimize to a very high degree the burden of the disease.

    2. There are effective treatments available, that can cure or minimize to a high degree the burden of the disease, however, they might cause certain side effects.

    3. There are certain effective treatments available that might ease the burden of the disease; however, they are not curative. Oftentimes, they cause relevant side effects.

    4. There are very few, if any, effective treatments available. There is virtually no cure and the treatments lead oftentimes to a serious array of side effects.

8. Clinical trials: completed or ongoing clinical trials regarding each condition.

9. Current academic output:  scientific production regarding each condition.

10. Overall assessment: brief assessment based on the data gathered. Two perspectives are covered: the business perspective, which addresses the market and financial potential; and the clinical perspective, which addresses the unmet clinical need around the particular condition.

For the search of relevant literature, I employed Scopus between the 1st of June, 2022 and 1st of September, 2022; the NCBI StatPearls collection – a peer-reviewed comprehensive medical database; references from relevant articles; medical information from the UK National Health Service (NHS) and US National Health Institutes (NIH) peer-reviewed medical websites (www.nhs.uk and www.nih.gov); and the services provided by GlobalData (GD), a UK-based data analytic and consulting company.

    1. The epidemiological data were gathered from scientific articles obtained through Scopus, StatPearls or the website of the NIH. Scopus searches would consist of "name of the condition" + "prevalence or incidence".

2. The trends in treatments and diagnostics, the assessment was based on information obtained from StatPearls, GD, and the NHS and NIH websites.

3. Burden of the disease: the disability-adjusted life-years (DALYs) for each condition were exclusively drawn from Vos et al. (2020). The additional information provided was based on StatPearls, the NHS, and NIH websites.

4. For the number of clinical trials for each disease, these were searched on clinicaltrials.gov. The searches were limited to:

    o Status: not yet recruiting, recruiting, enrolling by invitation, active – not recruiting, and completed.

    o Study type: interventional (clinical trial)

    o Study phase: phase 3 (exclusively when limiting the search to clinical phase 3 trials)

5. The current academic output was obtained from Scopus. The search would be limited to:

    o Articles title contains the name of the condition

    o Time range: 2010-2022

    o Document type: article

    o Language: English exclusively

6. For the discussion as well as the introduction all previously mentioned sources were employed.

Furthermore, several interviews were conducted with medical and scientific experts. I interviewed the experts to have a better understanding of two distinct questions: (1) the current diagnostic and treatment-related trends and problems in all these conditions and (2) the current trends and problems in the development of pharmacological therapies. The notes taken in these interviews are available under request. The interviews in cases 1 and 2 had the following core questions, although variations took place during the conduction of the interview.

Question 1:

1. How would you define ▮▮▮?

2. What are the most common cases you see in clinical practice?

3. Is it easy to diagnose? Or is it often misdiagnosed for other conditions?

4. Are there normally underlying conditions?

5. Are there environmental or social components that can trigger this condition?

6. What kind of treatments are available currently?

7. Does ▮▮▮ cause a significant burden on the patient?

Case 2:

1. In the development of drugs for (auto)immune/neurobiological conditions what are the main challenges you face?

2. Is the translation from basic science effective?

3. Are the pharmaceutical companies reluctant to invest in this type of research? Why?

# 4. Discussion

In the present report I have reviewed conditions that affect either the central nervous system or the immune system. The burden, the therapeutic and the diagnostic needs, and the prevalence and incidence of these conditions differs greatly. Hence, I have divided the discussion into the following sections: psychiatric conditions, neurodevelopmental conditions, sleep-wake conditions, neurodegenerative conditions, neurovascular conditions, migraines and epilepsy, allergic diseases, and autoimmune conditions.

## 4.1. Review of neurobiological conditions

### 4.1.1. Psychiatric conditions

Psychiatric disorders, oftentimes referred to as mental health disorders, have expressed a notable increase lately. For instance, Twenge et al. (2019) reported there has been an increase in mood disorders and suicidal outcomes since the mid-2000s. Similarly, Hedegaard et al., (2020) reported an increase in suicide in the United States between 1999 and 2018 for a total of 35%. And Goodwin et al. (2020) also reported an increase in anxiety among adult Americans. Hence, it is not surprising that the economic costs of depression alone – without including any other psychiatric condition – are estimated to be in the range of $300B per year in the United States (Greenberg et al., 2021; Twenge et al. 2019).

*Mood disorders and anxiety*

Among psychiatric conditions anxiety disorders (most remarkably generalized anxiety disorder or GAD, specific phobias, and obsessive-compulsive disorder or OCD) and depressive disorders are the most prevalent ones. They are fairly easy to diagnose as patients themselves normally tell what is happening to them.

Depression is a mood disorder that causes a persistent feeling of sadness and loss of interest that leads in the most severe cases to lose interest in life itself (Chand et al., 2022) and most severe cases are known as major depressive disorder (MDD) (**Table 1**). On the other side, GAD produces fear, worry, and a constant feeling of being overwhelmed (Munir and Takov, 2022). Oftentimes, both conditions are present together.  In fact, anxiety disorders and depressive disorders combined reach almost 70 DALYs in Western Europe.

| Type of MDD | Description |
|---|---|
| Melancholic depression | Loss of pleasure in all, or almost all, activities, or a lack of response to usually pleasurable stimuli. Somatic symptoms and psychomotor changes. The majority of patients with the melancholic subtype also have high levels of disease severity. |
| Psychotic depression | Depression accompanied by hallucinations and/or delusions that are usually, but not always, mood congruent. |
| Atypical depression | Characterized by mood reactivity and two or more of the following symptoms: significant weight gain or increased appetite; hypersomnia; leaden paralysis; and a long-standing pattern of sensitivity to interpersonal rejection (preceding mood disorder), causing significant social or occupational impairment. While atypical depression is a long-established concept, its essential features are still debated. |
| Anxious depression | Symptoms of anxiety and depression are both present, but neither is clearly predominant. |
| Suicidal depression | Patients demonstrate major depression with poor impulse control, despair, and hopelessness, and have historical risk of suicide. They require inpatient treatment. |
| Postpartum depression | Onset must be within four weeks of the birth. It is a full episode of major depression, not just the "baby blues," which are short-term drops in mood that usually pass within one to two weeks of the birth. It is also possible for new fathers to experience postpartum depression. |
| Seasonal affective disorder (SAD) | A form of MDD where onset and remission is triggered by a change of seasons. Typically, people experience SAD in the autumn or winter months, probably due to lack of sunlight. Some people can experience summer SAD, which seems to be caused by excess sunlight disrupting their circadian rhythm. |

**Table 1.** Subtypes of MDD (GlobalData, 2022)

Despite the available treatments for depression, one-third of depressed patients express treatment-resistant depression (TRD) (Ionescu et al., 2015), and as many as 17% of people with TRD attempt suicide. In addition, antidepressants and anxiolytics, drugs that are used in the treatment of both depression and GAD, can lead to severe side effects and withdrawal syndrome if the patient stops taking the medication rapidly (NHS, 2021).

Despite the obvious pharmacological needs in both conditions, and the elevated prevalence, the markets are flooded with drugs that lead to a very saturated market. In GAD, particularly, the market is inundated with over 95% of generic products, with less than 5% being innovator products (GlobalData, 2022). In addition, the drug pipeline for MDD consists of over 100 drugs and nearly 40% of these are in clinical trial phase II and above (GlobalData, 2022). Hence, I foresee an even more competitive environment as regards anxiety disorders and depressive disorders. The development of new therapies addressing symptoms would find a very hard time, and new therapies should be disease-modifying treatments (DMTs).

Alongside depression, bipolar disorder is another mood disorder that is characterized by manic or hypomanic episodes – periods of over-active and excited behavior – alternating or intermixed with episodes of depression (NIH). It is highly prevalent in the population with a yearly prevalence of 2.8%. However, unlike depressive or anxiety disorders it is a relatively hard condition to diagnose.

Bipolar disorder and borderline personality disorder are often confused. In addition, bipolar patients are also misdiagnosed with schizophrenia, especially in bipolar disorder type I, when the first clinical episode is mania (Jain and Mitra, 2022). Further, Philips and Kupfer (2013) addressed that bipolar disorder is often misdiagnosed as unipolar

depression, especially in patients who present during a depressive episode and in those with no clear history of mania or hypomania.

In this line, Philips and Kupfer (2013) also address that neuroimaging techniques, through analysis of abnormalities in white matter connectivity, abnormalities in grey matter, and functional abnormalities in neural circuitry, show particular promise to help identify neural circuit biomarkers that could aid in the diagnosis of bipolar disorder. Although the imaging domain lies outside Elithia's scope – it might still be of interest to NLC through its digital domain.

In the therapeutic field, the current gold standard to treat bipolar disorder is lithium. Lithium has the strongest evidence for long-term relapse prevention in contrast with anticonvulsants and antipsychotics (Geddes and Miklowitz, 2013) - in addition, lithium is a rather inexpensive product and its use is expected to continue (GlobalData, 2022). Also, there are many drugs currently authorized by the US food and drug administration (FDA) as shown by Butler et al. (2018).

This limits considerably the market potential for a new drug that is addressed at bipolar disorder, however, a biomarker in the field would be interesting, especially helpful to provide a differential diagnosis from depression, schizophrenia, and borderline personality disorder.

*Schizophrenia*

Among psychiatric disorders, schizophrenia is also highly prevalent in the general population and causes a rather high burden. The condition is characterized by affecting how a person thinks, feels, and behaves – people with schizophrenia may seem to have lost touch with reality, which can be distressing for them and those around them (NIH, 2022).

These symptoms can be broadly classified into positive (symptoms that are not normally experienced by other people but are present in schizophrenic patients, such as hallucinations) and negative symptoms (symptoms that are present in healthy individuals but are lacking in patients with schizophrenia, for example, lack of insight) (APA, 2013). Although a more precise diagnostic tool would be of interest, psychotic episodes are easily identifiable in the clinic.

There are many pharmacological treatments available to treat positive symptoms. However, negative symptoms are usually less responsive to medication. Due to lack of insight, patients are unaware of their illness and the consequences thereof. This way, patients fail to recognize the need for treatment, leading to poor treatment adherence (Buckley et al., 2007).

Nonetheless, the treatment pipeline is relatively small, given the large patient population and well-defined unmet needs, with a total of 160 products in active development (as of 2018). Still, there is a transition in the R&D landscape towards biologic products on an unprecedented scale (GlobalData, 2018) coupled with a large recent academic output. This suggests that there is a need for new treatments although

the current trend of symptom-based small-molecule treatment is already saturated and that the new age for biologics might have started.

*Eating disorders*

Within psychiatric conditions, another group of conditions widely present in western countries, and leading to a rapidly increasing market, are eating disorders. In this report, I have reviewed three of them: anorexia nervosa (AN) bulimia nervosa (BN), and binge-eating disorder (BED).

All three disorders are characterized by unhealthy eating habits; however, they are behaviorally very distinct. In AN, the patient will restrict the nutrient intake, leading to a potentially dangerous low body weight. BN is characterized by binge-eating but coupled with inappropriate compensatory behaviors such as vomiting or laxative consumption. Lastly, BED is characterized by binge-eating episodes – a large amount of food consumption in a short period of time.

Due to their behavioral pattern, AN and BED patients are easier to diagnose – patients usually present unhealthy low weight, while binge-eating disorders usually present obesity. Still, BED is a relatively new condition and has little social awareness. Therefore, patients tend to be diagnosed once they reach the physician's office for other conditions. Similarly, BN goes oftentimes unnoticed. Mainly because BN is not particularly observable, despite the somatic consequences the patients suffer. This leads, in BN, to suffer in silence.

In addition to the diagnostic difficulties – which could be sorted out by increasing awareness both on medical and societal levels – there are very few pharmacological treatments available. Currently, there is no pharmacological treatment approved for AN; for BN only the antidepressant fluoxetine; and for BED only lisdexamfetamine dimesylate, although antidepressants might be used off-label.

This leads to a rather limited pharmacological market. For instance, according to GD the pharmacologic market for 2027 in the 7 major markets (US, Japan, Germany, UK, France, Italy, and Spain) will reach for BED 417$m. Nonetheless, in my opinion, it shows a yet-unexplored market with considerable potential.

*Neurodevelopmental conditions*

Neurodevelopmental disorders (NDDs) are multifaceted conditions characterized by impairments in cognition, communication, behavior, and/or motor skills resulting from abnormal brain development (Mullin et al., 2013). In this report, I have reviewed four of them: attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), developmental learning disorder (DLD), and intellectual disability disorder (IDD).

Normally, the symptoms become visible when the environment, requires the patient certain attributes or attitudes and it is not able to meet them. In consequence, it is normally difficult to diagnose an NDD unless the patient finds himself or herself in that challenging context. Hence, the discovery of new biomarkers, either molecular or digital,

would help dearly in the early identification of patients with NDDs and provide support early on.

For instance, ADHD and DLD become visible in a school setting, when children are required to be attentive and quiet and have to learn to write, read and perform numerical calculations respectively. These disorders, while highly prevalent, are particularly present in the male population. For instance, only 0.9% of women suffer from ASD in contrast to 3.7% of men – similarly, ADHD is suffered by 3.2% of women and 5.4% of men. This coupled with the fact that girls tend to mask their symptoms can lead to underdiagnosis. Masking – or camouflaging – can be understood as a discrepancy between seemingly atypical, internalized social/cognitive abilities and seemingly neurotypical, externalized behaviors. For instance, autistic women are more likely to attempt to mask their autism and blend in with peers than autistic men (Halsall et al., 2021)

NDDs lack cure, and treatments in NDDs vary. For IDD, most support consists in adjusting the environmental and academic syllabus to the patient's needs. Similarly, for DLD, which encompasses dyslexia and dyscalculia, is supported by learning specialists who can help in dealing with the learning difficulties.

Still, in the case of ADHD, there are proven pharmacological treatments, although these are not effective in all cases (Martinez-Raga et al., 2017). Probably among ADHD medications, Adderall – an amphetamine – is the one that stands out the most. Hence, despite the need for better treatment, there is an already saturated market that might be difficult to enter as a small NLC venture. Nevertheless, I believe that new pharmacological treatments for ASD hold a better promise.

Current therapy is similar to that of IDD – environmental support and psychotherapy – and only two drugs are FDA-approved to be used in ASD – both antipsychotics employed to control irritability associated with ASD. However, there are no pharmacological treatments for the core symptoms of ASD: repetitive behaviors, limited interests, sociability, and communication problems, offering a large potential for new upcoming innovations. Still, ASD is a hot spot, with a very high recent academic output and currently two compounds in clinical trials phase III that appear to have the potential to help with these core behavioral problems: cannabidiol and butanamide (GlobalData, 2020).

### 4.1.2. Sleep disorders

*Insomnia*

When talking about SWD probably insomnia is the first condition that comes to mind of many. Insomnia is defined as the subjective perception of difficulty with sleep initiation, duration, consolidation, or quality, which occurs despite adequate opportunity for sleep, and results in some form of daytime impairment (Buysse, 2013). Insomnia is highly prevalent in the population. About 30% of the total population reports insomnia and

about one-third of these cases are chronic (Kaur et al., 2022; Momin and Ketvertis, 2022).

Despite these interesting epidemiological figures, the therapeutical market for insomnia is saturated. Currently, the first-line treatment is cognitive behavioral therapy for insomnia (CBT-i). CBT-i produces results that are equivalent to sleep medication, with no side effects, fewer episodes of relapse, and a tendency for sleep to continue to improve long past the end of treatment (Rossman, 2019). If CBT-i is not accessible or not effective, patients might still be prescribed hypnotic medication, commonly known as sleeping pills. There is a wide variety of these sorts of pills that would seriously limit the access of a new drug to the market.

*Disorders of hypersomnolence*

Among central disorders of hypersomnolence, narcolepsy is probably the best known. Narcolepsy is relatively rare, and it is characterized by excessive daytime sleepiness, frequent uncontrollable sleep attacks as well as sleep fragmentation. In addition, it can be associated with cataplexy, sleep paralysis, and hypnagogic hallucinations (Slowik et al., 2022).

There are two types of narcolepsy, type 1 which presents narcolepsy alongside cataplexy (sudden episodes of emotionally triggered muscle weakness), and type 2 – without cataplexy. Each type has a 0.014% and 0.065% of prevalence, hence, type 1 alone, would be considered a rare disease on its own (Slowik et al., 2022; Burgess and Scammell, 2012). Despite the low prevalence, the narcolepsy market is expected to grow by 2027 to $3.5B (**Figure 2**).
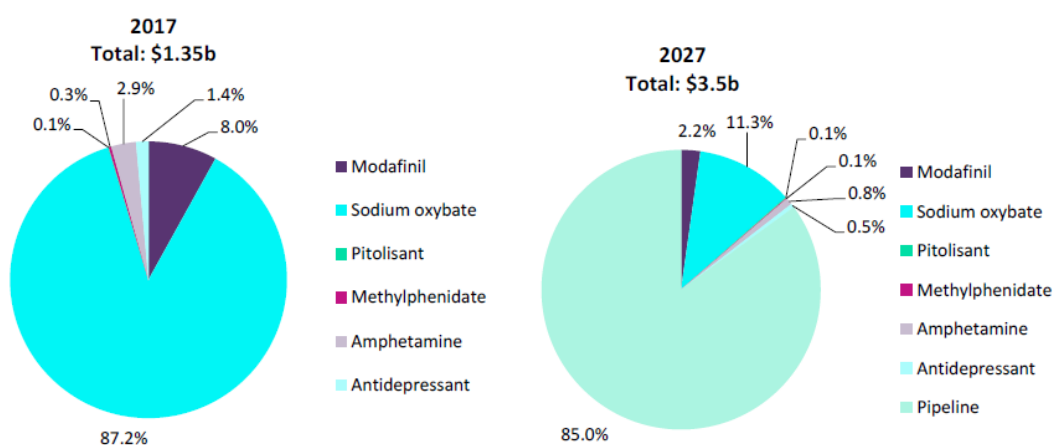


**Figure 2.** Forescasted increase in the market size from 2017 to 2027 and the share of the market each marketed compound takes (GlobalData, 2018)

The main unmet need in narcolepsy can be found in the diagnostic field. The diagnosis of narcolepsy can be a difficult feat as there is limited awareness even among clinicians which leads to misdiagnosis or underdiagnosis of narcolepsy patients (GlobalData, 2018). Currently, the only test available is a lumbar puncture to confirm narcolepsy type 1, however, a lumbar puncture is highly uncomfortable and can have serious

complications. In addition, it has no use to diagnose type 2, which is the most prevalent type. Hence, along with awareness campaigns, new improved diagnostic tests, such as molecular biomarkers, are needed.

However, the diagnostic field is not the only unmet need in narcolepsy. The condition has no cure, and the current first-line treatment is counseling for sleeping habits, such as the recommendation of short naps and having good sleep hygiene. Although there are several pharmaceutical compounds available, their efficacy is limited.

*Sleep-related breathing disorders*

The two main sleep-related breathing disorders are obstructive sleep apnea (OSA) and central sleep apnea (CSA)

Although the etiology of these two disorders is different, they are similar as regards symptomatology. OSA is caused by anatomic factors that lead to a complete or partial collapse of the upper airway during sleep (Slowik et al., 2022). On the other side, CSA is caused because the brain's breathing stimulus is halted during short period of times, causing irregularities in the breathing (Rana and Sankari, 2022).

Although OSA's prevalence is far superior to that of CSA's, it is not interesting to Elithia since the causes of the condition are anatomic rather than neurobiological.

CSA, despite being less prevalent than OSA, is quite present with a 0.9% prevalence, leading to a considerable market size. The condition presents needs both in the diagnostic and therapeutic fields. I believe that the therapeutic field would be particularly for Elithia. Currently, the CPAP machine is considered as first-line treatment, however, this machine has a low adherence rate. On the pharmacological side, acetazolamide is the only drug currently approved by the FDA.

Still, there is also a remarkable need in the diagnostic area as it can be challenging to diagnose based only on the symptoms. Patients might need to undergo nocturnal polysomnography (PSG) since its symptoms are shared with other conditions (ref). Hence, a biomarker would considerably help.

*Circadian-rhythm sleep disorders (CRSDs)*

Assessing the market and financial promise that CRSDs is difficult. There are several CRSDs (**Table 2**) and the prevalence of each of CRSDs is unknown – still the literature suggests it to be high (Kim et al., 2013).

| Disorder | Clinical features |
|---|---|
| Delayed sleep phase type | Sleep and wake times are delayed (later) compared to normal individuals and desired times, with striking inability to fall asleep and wake earlier at the desired time |
| Advanced sleep phase type | Sleep and wake times advanced (earlier) compared to normal individuals and desired times, with striking inability to remain awake and remain asleep until the desired time |
| Irregular sleep-wake type | Unrecognizable pattern and disorganized sleep and wake times, with insomnia and/or excessive daytime sleepiness |
| Free running type | Gradually delayed bedtime by 1-2 hours a day with insomnia and inability to wake in the morning |
| Jet lag type | Inability to fall asleep and wake at times compatible with desired times due to recent travel to new time zone. |
| Shift work type | Inability to fall sleep (during the day) and remain awake (at night) at times required for work schedule. |

**Table 2.** International Classification of Sleep Disorders categories of Circadian Rhythm Sleep Disorders with typical clinical features (Kim et al., 2013)

The diagnosis is usually easy and based on patients' complaints. Although pharmacological treatments might be needed occasionally, many cases are transient, and healthy lifestyle changes are enough, leading to a slow potential for Elithia to step in from the unmet need perspective.

*Parasomnias*

Parasomnias are a group of disorders that cause disruptions to the sleep cycle, either during continuous sleep or upon the transition to wakefulness (Fariba and Tadi, 2018). Here I have reviewed sleepwalking, sleep terrors, and sleep paralysis. Despite the high prevalence in society, they present almost no medical need – there is no long-time effect observed to any of them and they do not cause either disturbance in the daily functioning of the patient. The only one that may carry medical risk is sleep-walking should the patient carry out dangerous activities while asleep. With adequate preventive and environmental measures, it can be easily sorted out.

### 4.1.3. Neurological conditions

*Neurodegenerative and motor disorders*

Neurodegenerative diseases represent a major threat to human health. The prevalence of neurodegenerative disorders is increasing, owing — in part — to extensions in lifespan (Heemels, 2016).

Alzheimer's disease (AD) and Parkinson's disease (PD) are the two most common neurodegenerative conditions, with a prevalence of 2% and 0.2% respectively. AD can be defined as a slowly progressive neurodegenerative disease as a result of amyloid plaques in the medial temporal lobe and neocortical structures (Breijyeh and Karaman, 2020). On the other hand, PD is a neurodegenerative disorder that mostly presents in later life with generalized slowing of movements, and tremors and/or rigidity (Zafar and Yaddanapudi, 2021).

Both conditions face challenges in therapeutics and diagnostics. Both are difficult to diagnose – the diagnosis usually comes after the exclusion of several other conditions since there is no biomarker, laboratory test, or imaging technique that enables physicians to diagnose them rapidly.

Currently, AD diagnosis is dependent on clinical suspicion in primary care, and it is prone to be missed. In addition, once the symptoms arise, the condition is in an advanced state (Bradford et al., 2009). However, a new era of research might have stated – promising cerebrospinal fluid (CSF) represent a cost-, time-, and resource-effective approach with the potential to improve clinical practice in AD globally. However, CSF is obtained through lumbar puncture, a procedure that is prone to complications and discomfort in the patient. Hence, further refining in the field of biomarkers is needed.

As addressed by Breijyeh and Karaman (2020) the success of AD treatment depends on its early administration and patient monitoring for disease progression. Yet, current pharmacological treatments remain symptomatic, without alteration in the disease's prognosis. Treatments improve memory and alertness but do not prevent progression. Even though the total addressable market through a disease modifying therapies (DMTs) for AD would easily reach several billions of euros, there is a very competitive pipeline. There are 143 drugs in the AD drug development pipeline (**Figure 3**) and 83.2% of the candidate treatments are DMTs (Cummings et al., 2022).

**Figure 3.** Current AD drug development pipeline (Cummings et al., 2022).

In the case of PD, despite the lower number in prevalence than AD, the ageing population in western countries ensures a flourishing market. Just like in AD, it is difficult to diagnose PD in primary care. In the case of PD, a differential diagnosis from other parkinsonian syndromes and tremors is necessary (Zafar and Yaddanapudi., 2021).

One of the most important innovations in the diagnostic area of PD relies on the ability to identify forms of α-synuclein prone to aggregation, which represents a revolution in the diagnostics of synucleinopathies. These forms of α-synuclein would be identified via CSF or blood samples. Evidence suggests potential diagnostic and prognostic value of CSF and blood biomarkers closely reflecting the pathophysiology of Parkinson's disease. Still further validation in large independent cohorts is needed (Parnetti et al., 2019).

Currently, PD has no cure and in the treatment field there are very few drugs available. The majority of current pharmacological treatments for PD were approved for clinical use in the second half of the last century and they only provide symptomatic relief for a relatively short period of time. Nevertheless, there is a broad pipeline of both

symptomatic and DMTs currently being tested in clinical trials (Mcfarthing et al., 2021) – there are 28 phase 3 trials, of which two are DMTs.

Among motor-disorders, essential tremor is the most common neurologic cause of postural or action tremor (5% prevalence). Although ET is benign, it often causes embarrassment and, in a small percentage of patients, serious disability. Diagnosis in ET is based on excluding distinctive tremor types rather than asserting what tremor of ET, in other words, the diagnosis of ET has been largely one of exclusion (Espay et al, 2017).

Although the diagnostic field presents the largest unmet need, there are also unmet needs in the therapeutic field. Evidence shows that propranolol and primidone – which are considered first-line treatment – are not helpful for 30-50% of patients (American Academy of Neurology, 2011). Despite the need, the genetic etiology or molecular targets are unknown. Hence, much research is needed to develop new drugs – mostly DMT – for ET.

Similarly, I consider that tic disorder, or Tourette's syndrome (TS) on its most severe form, is of no interest to Elithia and NLC.  Tics are common hyperkinetic movement disorders seen mostly in the pediatric age group. These tics are sudden, rapid, recurrent, nonrhythmic motor movements or vocalization, generally preceded by urge (Jones et al., 2022).

Even if tics are common, most cases are mild and transient, hence the need in these cases is minimal. Around 60 percent of kids will, to some extent, reduce the tics they suffer. Half of these will outgrow them. Clinicians will only employ pharmacological treatments in most severe cases of TS or tic disorder when the tics can interfere with patients' life (Jones et al., 2022).

*Epilepsy and migraine*

Epilepsy and migraine are two chronic neurological conditions that are known to cause severe disability in those who suffer them. In particular, migraine has the bad reputation of being the second most disabling condition after low-back pain (Vos et al., 2020).

Migraine is a highly prevalent disorder characterized by episodes of moderate-to-severe headache, most often unilateral and generally associated with nausea and light and sound sensitivity and it is highly prevalent (Pescador Ruschel and De Jesus, 2022).

Migraine is easy to diagnose only based on the symptoms due to the intense hemicranial pain and the sensitivity to light and noise, although some tests might be performed to rule out any other potential condition. Hence, the unmet needs of this disorder lie in the therapeutic field.

The drugs employed in migraine can be classified as prophylactic or abortive. Prophylaxis requires daily administration of anti-migraine compounds – whether a migraine attack is occurring. However, these compounds have potential and often relevant side-effects. Hence, patients often reject the idea of preventive care or may lead to poor treatment adherence (D'Amico and Tepper, 2008).

Among abortive treatment, the most traditional options include non-specific analgesic such as non-steroidal anti-inflammatory drugs (NSAIDs). Ibuprofen is probably the most used and best known NSAID compound. In more severe cases, treatments also include triptans, ergot alkaloids and ditans (Noor et al., 2022). However, it is advised to take the medication at the first sign of the migraine attack, as it is too late for the drug to work (NHS, 2021)

In the case of epilepsy – a condition that causes frequent seizures, i.e., uncontrolled electrical disturbances in the brain that can affect behavior, mobility, feelings, and consciousness – the main need lies in the diagnostic field. It can be hard to diagnose epilepsy quickly because other conditions, such as fainting, migraines and panic attacks, can cause similar symptoms. It often cannot be confirmed until the patient has had more than 1 seizure. Electroencephalogram – which is considered as the main epilepsy biomarker – can be used to check brain activity – however this test is not definitive, and epilepsy might be diagnosed based solely on the symptoms (Huff and Murr, 2022).

Hence, the development of a new biomarker would be interesting. In addition, the academic output around epileptic biomarkers remains somewhat low with 143 scientific articles being published in the last 12 years. Nevertheless, there is an increasing trend as the last four years (2018-2022) account for more than half of the articles.

As for the therapeutics, although there is still an unmet need, it is a more competitive environment than the diagnostic one. There are many treatments available, although these medicines, which are called anti-epileptic drugs (AEDs), work only in 7 out of 10 people. In addition, there are currently 54 drugs in the pipeline, of which 5 are in phase 3 (Epilepsy Foundation, 2022). Hence, the market is somewhat saturated and new treatment in the field need to offer a significant improvement to existing drugs – valproic acid in particular – to have any traction in the market.

*Neurovascular disorder*

The neurovascular term encompasses many conditions, although in the report I have reviewed two of them: cerebral aneurysms and ischemic stroke – also known as cerebral ischemia.

A brain aneurysm is a berry-shaped bulge in an artery in or near the brain. An aneurysm develops when part of an artery wall becomes weak, stretches outward, and forms a bulge (InformedHealth.org, 2018). Aneurysms are very common – worldwide prevalence is in 3.2% – leading to a big market size (Jersey and Foster, 2022). However, there is no pharmacological treatment to deal with them and surgical tools are the only thing available, and these surgical methods entail risks (NHS, 2022)

In addition to the lack of pharmacological treatments, aneurysms can be misdiagnosed or not diagnosed at all, in particular among smaller aneurysms. Smaller aneurysms may not present any symptoms at all, hence misdiagnosis or delayed diagnosis is not rare. In fact, most unruptured cerebral aneurysms are identified incidentally when a patient gets neuroimaging for some other reason. (DeSai and Shapshak, 2022 and Sveinsson et al.,

2014). However, once a cerebral aneurysm ruptures, morbidity and mortality are very high. Nearly 25% are dead within the first 24 hours, and 50% will die within the next three months (Jersey and Foster, 2022).

When talking about strokes normally they are classified in two groups: hemorrhagic strokes in which a blood vessel bleeds and ischemic strokes, when blood flow is impaired in the brain, which are actually far more common. Ischemic strokes account for 87% of all strokes and have an incidence of 210 per 100.000 cases (CDC, 2022).

Ischemic strokes are imminent cause of medical emergency due to the limited time frame in which specialists need to operate. Its diagnosis can be challenging as it can be confused with other neurological conditions. While the imaging technique show whether there is ischemic tissue or not, there is no biomarker that enables clinicians to diagnose ischemia, slowing down the diagnostic process. The fact that misdiagnosis or delayed diagnosis might take place makes the treatment difficult and the prognosis worse. In fact, the majority of patients do not receive thrombolytic therapy due to late arrival to emergency departments and currently there is a paucity of acute interventions for them (Bansal et al., 2014).

Currently, there is only one FDA-approved drug, alteplase, however it needs to be administered within the first 4.5h the ischemic stroke took place (DeSai and Shapshak, 2022). Hence, it is necessary to develop new drugs that target ischemia both in early moments and later ones.

## 4.2. Review of immunological conditions

### 4.2.1. Allergies

Allergies are exaggerated responses from the body's immune system to otherwise inert substances present in the environment and triggers a reaction from the body's immune response described as hypersensitivity (Dougherty et al., 2021) allergies are very prevalent, leading to a wide market, although there are many types of allergies and there is a large variability between them. It is impossible to cure them, and most trends go towards prevention and treating symptoms if they have taken place. Still, desensitization and immunotherapy are used in certain cases successfully.

On the other side, the severity itself can vary. Generally, they will not affect the patients' daily life unless they are in contact with the allergens. Further, occasionally patients can have spontaneous resolution from mild symptoms, although in most cases the symptoms will progress in severity. Hence, in some instances, the impact or burden will be minimal, however in some cases allergic reactions, such as anaphylaxis, can be potentially fatal requiring immediate medical care. These anaphylactic reactions are mostly common via food or drug consumption. However, there are already ways to deal with this in both instances – for food allergies, patients normally have epinephrine autoinjectors – and in the case of drug allergies, doctors normally know it and avoid exposing the patient to the allergen.

Hence, needs in the allergic space lie mostly in the therapeutic field, in particular, regarding food allergies.

### 4.2.2. Autoimmune conditions

There are plenty of autoimmune conditions. After reviewing many of them, based on the unmet needs (therapeutic and diagnostic), the saturation or size of the market, the following should not be considered for a business case:

- Graves' disease: it is the most common cause of hyperthyroidism with systemic manifestations that primarily affect heart, skeletal muscle, eyes, skin, bone, and liver. Despite the high prevalence, and the market that could potentially stem from there, it is easy to diagnose and there are many treatments available, leading to saturated market. Some of these treatments might lead to hypothyroidism and preventing this from happening would be interesting, still hypothyroidism is easy to treat.

- Hashimoto's disease: it is one of the most common causes of hypothyroidism. This leads to symptoms of an underactive thyroid gland (hypothyroidism), such as tiredness, weight gain and dry skin. However, it is easy to diagnose and to treat.

- Psoriasis: it is a chronic proliferative and inflammatory condition of the skin that can occasionally also affect the joints and eyes, in addition is one of the most prevalent autoimmune conditions. However, despite the lack of cure, the market is saturated, and it is easy to diagnose just based on the symptoms and skin rashes.

- Diabetes type 1: in a similar vein to that of psoriasis, the market is extremely saturated in every sense. Production of insulin has been optimized over the last decades and there are many devices that allow to monitor continuously the levels of sugar in blood. In addition, improvement in this field would be out of Elithia's scope, although they could be of interest to the med-tech or digital domains.

- Alopecia areata: This is a form of alopecia that impacts hair follicles, nails, and rarely, the retinal pigment epithelium. The market is limited due to its low prevalence. In addition, despite the lack of treatment, it does not pose any relevant health risk, and its burden is minimal when compared to other conditions. The main burden is emotional one.

- Vitiligo: vitiligo is a common acquired skin disorder which results from the loss of melanocytes from the epidermis and clinically manifests as well-demarcated white patches on the body. Despite the relatively elevated prevalence, it has a low burden and normally not treatment is needed as complications are rare. The main burden is emotional one.

Nevertheless, I believe there are many autoimmune conditions with clinical unmet needs in which Elithia could make a difference. One of these is celiac disease (CeD). CeD,

also known as gluten-sensitive enteropathy, is an autoimmune condition of the small intestine in which the body responds to gluten with an inappropriate immune response causing small intestinal inflammation and damage (ref). It is quite a common condition with a 0.5-1% prevalence (Posner and Haseeb, 2022)

In CeD the main market opportunities are around the diagnosis. It can sometimes be difficult to perform a differential diagnosis (**Figure 4**).
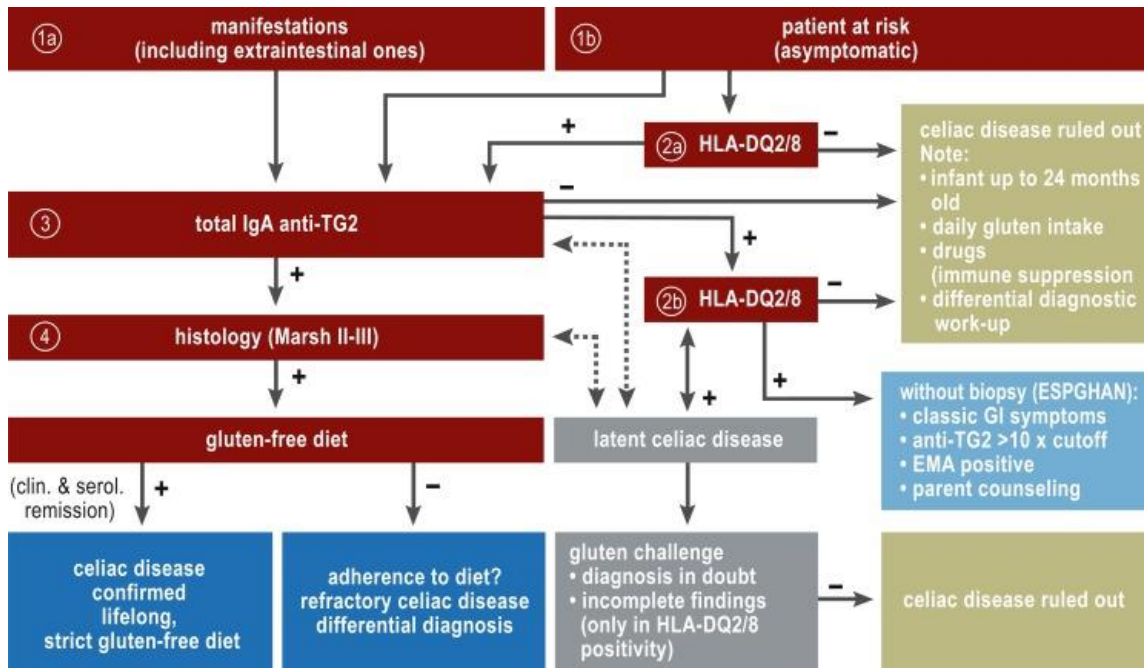


**Figure 4**. The figure shows the complicated decision flowchart in the diagnosis of celiac disease (Schuppan and Zimmer, 2013).

Endoscopy with duodenal biopsy showing villous atrophy (named histology in the flowchart) is the current gold standard for diagnosing CeD, but the procedure is invasive and accompanied by a risk, albeit small, of abdominal pain, bloating, discomfort, bleeding, or perforation. Thus, identifying noninvasive tests that are accurate and have few or no side effects is important (John M. Eisenberg Center for Clinical Decisions and Communications Science, 2007)

Unlike CeD, systemic lupus erythematosus (SLE) is a relatively rare condition with a 0.07% prevalence. SLE is a multisystemic condition that causes inflammation of different parts of the body including, but not limited to, the lungs, heart, kidney, liver and joints. Although prognosis and mortality has improved in recent years, people from sub-Saharan origin and women have more often SLE with a worse prognosis.

The condition presents needs both in the diagnostic and therapeutic field. Currently, there is no cure and there are only two FDA-approved drugs. Nonetheless, there is a fairly competitive drug pipeline as our understanding of the pathogenesis of the disease has advanced (Klavdianou et al., 2020).

Furthermore, there is no biomarker or concrete laboratory technique that enables clinicians to diagnose SLE, and often, it is misdiagnosed for other autoimmune disorders.

SLE diagnosis currently relies on a combination of clinical features and laboratory tests (Tsokos, 2016). However, early diagnosis of lupus is essential to prevent organ damage. Partly, because of this lack of effective diagnostic tool SLE can take a big toll on the patients. Moreover, the need for biomarkers is not limited to the diagnosis exclusively, such as activity biomarkers to examine SLE disease activity, biomarkers to detect specific organ involvement and theranostic biomarkers to predict treatment response (Tsokos, 2016)

Another autoimmune condition that I have reviewed is rheumatoid arthritis (RA) which is characterized by inflammatory arthritis and extra-articular involvement, causing pain, swelling, and stiffness in the joints. The condition usually affects the hands, feet and wrist. It is somewhat common with a 0.46% of global prevalence (Almutairi et al., 2021). It is particularly problematic in the field of diagnostic because of the lack of biomarkers and the many conditions that can cause joint stiffness and inflammation. Hence new diagnostic biomarkers would be dearly appreciated. Still, the is no cure either. There are several FDA-approved DMTs that help prevent or minimize the impact of RA. These drugs are used as first-line treatment and are known as disease-modifying anti-rheumatic drugs or DMARDs.

Instead of causing inflammation in the joints, inflammatory bowel disease (IBD) provokes inflammation of the gastrointestinal track. It is a chronic disease, and it actually refers to two different pathologies: Crohn's disease (CrD) which is characterized by skip lesions and transmural inflammation that can affect the entire gastrointestinal track from mouth to the anus, and ulcerative colitis (UC) involves inflammation that mostly affects the colorectum (Feuerstein and Cheifetz, 2017; McDowell et al., 2022).

IBD is quite common with a prevalence of 1% (Ghosh et al., 2015) and UC is more common than CD (Pasvol et al., 2020). Despite both conditions are classified as IBD the treatment is different: as regards UC, it is usually more benign than CrD. Less severe cases can go untreated with just the patient being monitored and taking certain precautions. However, it can worsen, and 1 in 5 patients will be resistant to treatments and will need surgery to remove an inflamed section of the colon.  On the other hand, it is estimated that 70% of CrD patients will require surgery (McDowell et al., 2022). However, despite the needs in therapeutics, especially for CrD, there are several drugs in the therapeutic pipeline (Grossberg et al., 2022)

In addition, IBD can sometimes be difficult to diagnose because it can have similar symptoms to lots of other conditions (NHS, 2021). Still, stool biomarkers are useful although they might not be enough, and colonoscopy or biopsies need to be performed.

## 4.3.    Last remarks

The unmet needs in the fields of diagnostics and therapeutics can differ greatly from one condition to another. Some are easy to diagnose and require little effort from the clinician, such as migraines or psoriasis. Other conditions might have a plethora of pharmacological treatments available or have minimal impact on the patients' well-being, such as Grave's disease and sleep-walking respectively. Sadly, in other cases it can

be the complete opposite, such as in Alzheimer's disease, where diagnosis is difficult, it usually comes delayed and current pharmacological treatments are purely symptom-oriented and do not halt or slow down the progress of the disease.

After reviewing these conditions, I believe that the diagnostic via biomarkers is the spot with the greatest potential for Elithia and where NLC will be able to make a considerable impact on society.

In the field of psychiatry bipolar disorder patients and those suffering neurodevelopmental disorders would benefit the most. Bipolar disorder is often misdiagnosed for schizophrenia, depression and borderline personality disorder – these leads to a delayed adequate treatment administration and affect the development of the patient.

Among SWDs, central sleep apnea and narcolepsy also face similar challenges due to the similar symptomatology with other conditions and the lack of awareness among clinicians, respectively. In neurology, biomarkers for PD, AD and epilepsy would allow clinicians to act early on in the disease. Across autoimmune conditions, differential biomarkers would help given the fact that autoimmunity and inflammation are symptoms shared by many disorders.

However, the speed in biomarker research and development is unequal. Biomarker research is a rapidly advancing area in autoimmune disease. Several studies have been conducted to discover new biomarkers including autoantibodies in autoimmune conditions (Shi et al., 2017).

Similarly, in the field of neurology, biomarker research has also advanced in the latest years. In AD, promising CSF biomarkers have gained some attention to diagnose it as a large number of clinical studies very consistently show that these biomarkers contribute with diagnostically relevant information, also in the early disease stages (Blennow and Zetteberg, 2018). However, to obtain CSF it is necessary to carry out a lumbar puncture, which is an invasive procedure. Hence, there is an ongoing effort to find new biomarkers through less invasive means such as blood samples or neuroimaging (Villa, 2020). And in PD there is a growing hope around microRNAs, in addition to conservative approach based on the identification of new protein biomarkers in blood, plasma and CSF (Fyfe, 2020; Emamzadeh and Surguchov, 2018).

Still, in the field of mental health there is a lack of biomarker investigations especially related to treatment response, although advances in electrophysiology, neuroimaging, genetics, transcriptomics, proteomics, metabolomics, and epigenetics, throw some hope that it will enable researchers to develop new biomarkers (García-Gutiérrez et al., 2020; Jeste et al., 2015).

# 5. Conclusions

The unmet needs vary considerably from one condition to another. However, the diagnostic field seems to hold a lot of potential. Currently, many neurobiological and immunological conditions are difficult to diagnose. Lack of medical awareness, similarity with other conditions, and the lack of diagnostic biomarkers are some of the reasons. Hence, many patients receive the treatment delayed, the wrong one, or no treatment altogether. This causes a significant burden on society, which could otherwise be mitigated.

New biomarkers, either molecular or digital, would help in patients in being diagnosed earlier and hence receiving the adequate treatment in time. This report shows that the diagnostic field holds great promise for NLC, as the diagnostic market of many of these conditions can be classified as a blue ocean.

# 6. Future trends

Research in the fields of neurobiology and immunology is moving forward fast, however, further academic research is needed to understand the pathophysiology of these conditions and develop adequate diagnostic biomarkers and therapeutic tools.

As regards NLC, NLC is following the right path with the Elithia fund in its attempt to tackle the unmet needs in the fields of neurobiology and immunology. Still, this report is a disease mapping that contains only 40 conditions. There is a plethora of neurobiological and immunological conditions with big unmet needs, but due to its low prevalence and the usual limitations of an internship report have not been included. In particular, orphan diseases have high levels of unmet needs. Hence, I believe that the Elithia team needs to further expand this list to understand all the unmet needs surrounding each condition and find new markets where NLC can make a positive impact in society.

Further, this sort of report not only is useful to the Elithia team, but also to NLC as a whole. Although this report is focused on biotechnological solutions, i.e., molecular biomarkers and drugs, there is a lot of potential in the digital domain where digital biomarkers obtained, for instance, via MRIs or CT scans can also help in the diagnostics.

# 7. Management summary

## 7.1.     Problem statement

There are plenty of medical conditions, each of them with its own unmet medical needs. Elithia, NLC's most recent fund, in focused on neurobiological and immunological conditions. However, the unmet needs of many of these of many of these conditions remain unknown to the team.

## 7.2.     Proposed solution

A disease mapping of the CNS and immune system, encompassing conditions that could be classified as neurobiological, immunological, and neuroimmunological. This will help shed light on the current diagnostic and therapeutic gaps in neurobiological and immunological conditions. Furthermore, the information gathered for the review of each condition is organized in fact-sheets – this way, the data, and findings are more accessible to the Elithia team.

## 7.3.     Methods

The data employed in this report has been obtained from peer-reviewed sources such as Scopus or the NCBI StatPearls collection. This data has been organized in fact-sheets on which the discussion is based. In addition, interviews to experts were conducted.

## 7.4.     Conclusion

The unmet needs vary considerably from one condition to another. However, the diagnostic field seems to hold a lot of potential. New biomarkers, either molecular or digital, would help in patients in being diagnosed earlier and hence receiving the adequate treatment in time. In addition, the biomarker market for many of these conditions can be classified as a blue ocean, holding a considerable financial potential as well.

## 7.5.     Future trends

Further academic research is needed to find more diagnostic and therapeutic tools. The pathophysiology of many conditions is not fully understood yet, and that limits the potential of obtaining new and accurate biomarkers. In addition, this is a brief disease mapping that contains about 40 conditions. I recommend both NLC and the Elithia team to further expand this list to understand all the unmet needs surrounding each condition and find new markets and opportunities where NLC can make a positive impact in society.

## 8. Personal experience

When I started thinking about how I would start writing this report, I did have no idea – honestly. Probably, because I didn't know what to expect at the internship, either. Transitioning from college to an actual company felt in the beginning a bit odd and still in the first month I didn't have the feeling I was actually working. I was, in a way, getting used to a new environment.

I would look at my co-workers, feeling they were superior – a level up, and although that's to some extent true, I could see NLC makes an effort to minimise that impact as much as possible. Nonetheless, I had to struggle with that feeling quite throughout my internship. But after all, they were just a bunch of (nice and occasionally alcoholic) people swimming together towards a common purpose – that of innovation to improve health. To give my best, I had to be part of that team, rather than an outsider that tries to work from the distance. Yet, once again, I struggled.

Although I tried to ignore these facts about myself – maybe even lie to myself –, those I worked closely with in the beginning (Jordy, Kathrin, and Dominique) realised. And they did an excellent job in being blunt (in a Dutch way – whether that's good or bad, I'll leave it to your imagination) and telling me about it. They acknowledged my hard skills and capacity to digest complex information (5 years of biotech and neuroscience education are useful after all), but most importantly my drive. My proactivity. My will to take as many projects as possible despite being drowned in a pit of workload (due diligence, quickscans, SIPs and BOEs, the dreaded puppy, etc.). I agreed. But I also agreed that I needed to improve.

The feedback they provided was honest and straight to the point. My communications skills – especially those in a commercial setting, weren't my strongest suit. And also, my unstructured way of thinking was sometimes bothersome – having 80 thoughts in my mind and losing track of them all at the same time is not ideal.

After this mid-term review, I was 100% sure I wanted to improve, but (once again) my insecurities kicked in and I didn't know whether my learning curve would meet my team's expectations. I tried to work harder, take more ownership, take notes carefully and organise my meetings better – so I would not lose track of my thoughts. I was worried, but eventually I forgot. I kept rolling, having integrated many of the points from the mid-term feedback without having even realised. I got the hang of many things I'd been unable to handle in the beginning.

Here, my team's support was essential. The human quality, the extremely healthy working environment, talking to Annameta or Christine about my insecurities, the repetitive yet necessary question "do you need support" and many other things dearly helped. And, well, the way my supervisor – Jordy Breuker – managed me was on point, especially towards the end. He wouldn't be the usual supervisor or mentor looking at the quality of every bit of work I would do – he'd be hands-off, without micromanaging, but available when I would need him. The line "Hey Jordy, just a catch-up with a coffee.

If you cannot make it feel free to reschedule" (or similar ones) would pop up every couple of weeks on his Google Calendars, and he would simply accept them.

But, if I had to pick one thing that has helped grow, it'd be the "interdepartmental jumping". In my last two months, I wanted to see where my strengths aligned more. As such, I ended up in the Technology Sourcing team, in the Technology Assessment and Strategy team, and in the Tech Partnership team. Probably I drove Jordy a bit mad during those two last months.

Despite everything I just said, this doesn't mean I have changed how I am – I just grew up, both personally and professionally. And that's, my dear reader, how it is supposed to be.

Back, in my first year of my master's I wrote this bit – much to the disappointment of my at-that-time supervisor and PI:

> *A common misconception in academia is that students must hand in perfect reports, ignoring the limitations there might be, and the research they perform must be flawless. However, the aim should not be such, but to be allowed to fail (to some extent) and consequently study from their own mistakes.*

Once more, I second my old words and add that I have been allowed to fail much more at NLC than at my former lab and, in consequence, I've learnt far more about me and my working style.

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