Navigating the Normal Pressure Hydrocephalus Landscape: A Product Development Strategy for a Neurodegenerative Diagnostic Startup

By

John Modarres

B.S. Biology, Duke University, 2022

Thesis

Submitted in partial fulfillment of the requirements for the Degree of Master of Science in the Graduate Program of Biotechnology at Brown University

Providence, Rhode Island

May 2025

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Date 4/29/2025 Signature: _____

Dr. Maria Grazia Ruocco, Advisor

Date 4/29/2025 Signature: _____

Dr. Eric Huang, Reader

Date 4/30/2025 Signature: _____

Dr. Mostafa Analoui, Reader

Approved by the Graduate Council

Date_____ Signature: _____

Dr. Thomas Lewis, Dean of the Graduate School

Acknowledgments

I am deeply grateful to Adelle Diagnostics for providing the invaluable opportunity to conduct this research and expand my understanding and skills within the biotech industry. I would especially like to recognize the exceptional mentorship and collaborative spirit of Dr. Maria Grazia Ruocco and Dr. Alexander Fleischmann; their guidance was instrumental throughout this entire process, and I am truly appreciative of the opportunity to have worked alongside them and Adelle Diagnostics.

I also extend my sincere thanks to Dr. Eric Huang and Dr. Mostafa Analoui for their insightful contributions and constructive feedback as members of my thesis committee, which significantly enhanced the quality of this work. My deepest gratitude goes to Dr. Jacquelyn Schell, whose unwavering advice and support touched every facet of this thesis and my M.S. journey as a whole. Her guidance has been truly invaluable.

On a personal note, I would like to thank my parents for their steadfast support throughout my master's studies and indeed, across all of life's milestones. Their encouragement has been a constant source of strength. Finally, I wish to acknowledge my grandfathers, whose significant presence in my life and experiences with neurodegenerative diseases served as a powerful inspiration for this research. Their memory has been a driving force behind this endeavor.

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Abstract

This thesis investigates the optimal product development strategy for Adelle Diagnostics, a neurodiagnostic startup from Brown University developing the Shunt IQ test to predict the efficacy of Normal Pressure Hydrocephalus (NPH) shunt surgery. Amidst a competitive neurodiagnostic landscape and challenging funding environment, the central research question explores the characteristics required for a diagnostic tool to achieve financial success. The study evaluates the hypothesis that focusing on the NPH shunt prediction application, enhancing intellectual property (IP), and pursuing potential licensing offers is the most viable path for Adelle.

A mixed-methods approach combined quantitative competitive analysis of 89 startups with qualitative analysis of high-performing outliers and 26 Key Opinion Leader (KOL) interviews guided by I-Corps principles. Statistical analysis revealed patent quantity and employee count as strong predictors of startup valuation and capital raised, supporting the IP-centric hypothesis. Qualitative analysis highlighted higher valuations for companies with diversified portfolios and the risks associated with single-asset pipelines.

KOL interviews confirmed a significant unmet need to predict NPH shunt efficacy and a substantial, underdiagnosed NPH market. While enthusiasm exists for biomarker diagnostics, a strong preference for less invasive methods over CSF was noted, though CSF analysis via ShuntIQ may be justifiable pre-shunt. Key recommendations include rigorous clinical validation and robust IP protection for ShuntIQ, prioritizing developing a blood-based assay if feasible, maintaining strategic focus on the NPH indication given market conditions, and actively exploring strategic partnerships. This strategy aims to optimize Adelle's clinical and financial success potential by addressing a clear market need while navigating resource constraints.

Chapter 1: Introduction

1.1 Primary Research Goals

Adelle Diagnostics is a neurodiagnostic startup founded in 2021 at Brown University by Dr. Maria-Grazia Ruocco as the principal founder and CEO. Adelle aims to pioneer biomarker discovery for neurodegenerative diseases by combining innovative molecular technologies and data science [1]. Central to this effort is the Diagnostic by Molecular Associations (DIMA) system, a software tool integrating molecular and clinical data with machine learning for identifying and validating molecular signatures. Leveraging this platform, Adelle is developing ShuntIQ, a Lab Developed Test (LDT) with the potential to more accurately predict the efficacy of shunt surgery, a procedure used to treat NPH [2]. While Adelle plans to develop and market this test for NPH patients, the founders are considering the possibility of expanding their platform to other indications, such as diagnosing or predicting treatment outcomes for other neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and other dementias [1]. With these goals in mind, the founders of Adelle are seeking guidance on navigating the neurodiagnostic clinical space effectively to optimize their chances of clinical and financial success.

During my work with Adelle, I undertook a comprehensive analysis of the neurodegenerative disease diagnostics market and clinical landscape. This research aimed to provide Adelle's founders with a clear understanding of their development options. My objective was to formulate a strategic product development plan that would help Adelle achieve financial success while remaining firmly rooted in its scientific research. To guide this endeavor, I focused on the central question: 'Given the current diagnostic landscape and market conditions, what

characteristics must a neurodiagnostic tool possess to optimize Adelle's financial success?' This investigation required a dual approach, encompassing both scientific and business perspectives.

As is customary for a thesis, I developed a hypothesis regarding the characteristics a successful diagnostic tool should possess. I hypothesized that Adelle should prioritize developing a test that can predict shunt efficacy while not being used for other indications to achieve financial viability. After this product has been developed, Adelle should also enhance the value of their technology's IP and potentially license it to a larger organization. This hypothesis was informed by the current scope of Adelle's research and by standard practices observed in early-stage university spin-offs. My research was designed not only to address the primary question but also to evaluate the validity of this proposed thesis.

To comprehensively address my central question, I employed two complementary methodologies to explore the diagnostic landscapes of NPH and broader neurodegenerative diseases. Initially, I conducted a competitive analysis of 89 startups to discern trends in disease targets, technological applications, and financial performance. I used raised capital and valuations as appropriate metrics of financial success, given their early-stage, pre-revenue status, which is similar to Adelle. Subsequently, I examined variables like technology categories, patent portfolios, and employee counts to identify potential correlations with financial outcomes. High-performing outliers from this quantitative analysis underwent a qualitative review of their technologies and business strategies to pinpoint factors contributing to their success. This combined quantitative and qualitative approach yielded crucial insights into the neurodiagnostic industry and the requirements for startup success. Complementing the analysis of emerging startups, I also examined the investment activities of 10 established biopharmaceutical giants within the NPH sector. This assessment aimed to determine their potential as competitive threats

or strategic partners for Adelle. Secondly, to understand the diagnostic and treatment pathways for NPH and dementia patients, I collaborated with Adelle to conduct interviews with key opinion leaders (KOLs). These experts, including neurologists, researchers, hospital administrators, patient advocates, NPH entrepreneurs, and an NPH patient, provided critical perspectives on current shortcomings, areas for improvement, and anticipated industry changes. Their insights were pivotal in delineating the necessary characteristics for a clinically and financially viable NPH diagnostic tool.

1.2 Understanding NPH

NPH is a neurological condition characterized by the accumulation of cerebrospinal fluid (CSF) within the brain's ventricles [3]. The buildup of CSF in the brain causes the brain's ventricles to be enlarged, which can subsequently exert pressure on the surrounding brain tissue and disrupt normal brain function [4]. While NPH causes an increase in CSF volume, the pressure of the fluid, as measured with a lumbar puncture, is normal or only slightly elevated, which is why the designation normal pressure hydrocephalus is used to describe this condition [5]. Interestingly, the term "normal pressure" can be misleading, as evidence suggests that individuals with NPH may experience periods of increased intracranial pressure [6]. Additionally, NPH is classified as a form of communicating hydrocephalus, indicating that the flow of CSF is

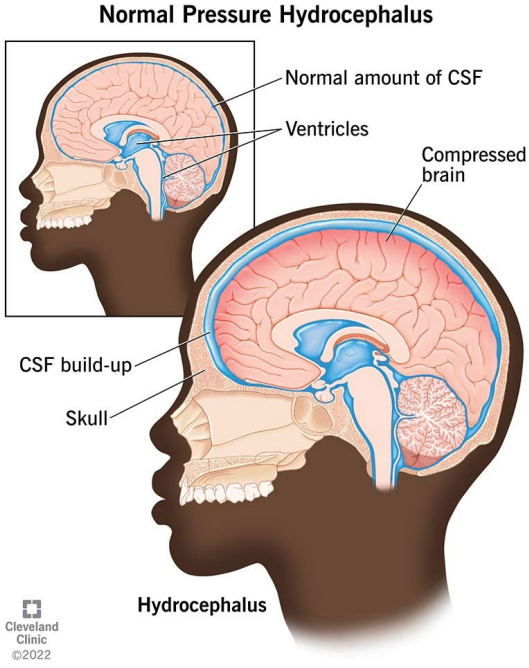

Figure 1 A graphic representing how an excess of CSF causes NPH [7].

obstructed after it exits the ventricles, while the ventricles themselves remain open [6]. This distinguishes NPH from non-communicating or obstructive hydrocephalus, where blockage occurs within the ventricular system itself.

While NPH can affect all ages, the condition primarily affects older adults, with the typical age of onset being 60 years or older [5]. NPH is widely regarded as an underdiagnosed disease where patients are often misdiagnosed as having other, more common neurodegenerative conditions, such as AD and PD [3]. This diagnostic challenge highlights the importance of a comprehensive understanding of the unique characteristics of NPH. Notably, NPH can contribute to roughly 5-10% of dementia cases in the older adult population, highlighting its clinical significance [5]. NPH is broadly categorized into two primary forms: idiopathic normal pressure hydrocephalus (iNPH) and secondary normal pressure hydrocephalus (sNPH) [7]. iNPH is characterized by the absence of any identifiable underlying cause for the development of hydrocephalus and represents the most common form of hydrocephalus in older adults [6]. The exact reasons behind the development of iNPH remain a subject of ongoing research and are not yet fully understood [7]. However, experts hypothesize that there may be age-related changes in the mechanisms governing the production and reabsorption of CSF that may play a role in causing iNPH [8]. Such changes may include a reduction in the compliance or elasticity of the subarachnoid space, the area surrounding the brain where cerebrospinal fluid (CSF) circulates before being reabsorbed [5]. In contrast to iNPH, sNPH develops as a consequence of a pre-existing medical condition or a specific event that affects the normal circulation or absorption of CSF [7]. These risk factors can include hemorrhage, traumatic brain injury, brain infection, a tumor, or radiation [6]. Given the various causes of sNPH, the disease can affect people of all ages [7]. The diverse range of identifiable causes in sNPH provides a clearer understanding of its

pathogenesis compared to the idiopathic nature of iNPH, leading to a more comprehensive understanding of the disease for physicians.

A significant reason why NPH is challenging to diagnose is that its symptoms vary significantly from patient to patient. However, NPH is usually characterized by a triad of symptoms, whereby the patient exhibits at least one. These symptoms are gait disturbances, cognitive impairment, and urinary incontinence [9]. Given the varying degrees in which these symptoms are presented in patients, it is no surprise that NPH is often misdiagnosed as unrelated diseases, including other dementias and even urinary tract infections.

NPH is a complex disease to diagnose, given the lack of knowledge regarding iNPH causation and the variability of symptoms. Therefore, diagnosing NPH requires a comprehensive evaluation that includes a detailed clinical assessment, neurological examination, neuroimaging studies, and cerebrospinal fluid analysis [10]. Diagnosing NPH usually requires specialized dementia centers, whereby the diagnostic procedure usually begins with a thorough gathering of a patient's medical history. This includes inquiring about the onset and progression of the three main NPH symptoms and other risk factors [11]. The medical history evaluation also looks for prior conditions that may lead to sNPH, including head injury, subarachnoid hemorrhage, meningitis, or previous brain surgery [10]. Next, a crucial component of the diagnostic process is the neurological examination [12]. The neurological examination for NPH involves assessing motor, sensory, and cognitive functions, with a focus on gait analysis to identify characteristic walking patterns [11]. Cognitive assessments, using tools such as the Mini-Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA), are crucial for evaluating memory, attention, and executive function, while also differentiating NPH from similar conditions, including PD and other dementias [13]. Imaging is also an essential step in

diagnosing NPH as technologies such as MRIs can visualize enlarged ventricles (ventriculomegaly) and assess CSF flow [7]. Distinguishing NPH from other forms of hydrocephalus relies on disproportionate ventricular enlargement relative to cerebral atrophy [6]. Specific MRI findings, such as enlarged temporal horns, periventricular changes, corpus callosum thinning, and an Evans index greater than 0.3, may suggest NPH [13]. However, imaging must be interpreted in conjunction with clinical symptoms for an accurate diagnosis [13]. The final component of an NPH assessment is CSF analysis, which is conducted via a lumbar puncture [13]. Normal or mildly elevated cerebrospinal fluid (CSF) pressure that occurs despite potential high resistance to outflow may be indicative of normal pressure hydrocephalus (NPH) [13]. Physicians also look for an improvement in symptoms when varying amounts of CSF are removed during a High Volume Tap Test (HVTT), which could also indicate that a patient has NPH. Physicians may also use this test to predict whether shunt surgery will be effective [13].

Unlike other neurodegenerative diseases, NPH can be effectively treated in many cases [7]. Shunt surgery is the primary intervention for NPH [7]. A shunt system, typically a ventriculoperitoneal (VP) shunt, is implanted via a surgical procedure and drains CSF from a brain ventricle to the abdominal cavity via catheters and a regulating valve [14,15]. While VP shunts are the most common and often effective for gait and bladder issues, ventriculoatrial (VA) shunts, draining CSF to the heart, are used when abdominal drainage is unsuitable. However, this comes with an increased risk of infection [15]. Ventriculopleural (VPL) shunts redirect excess cerebrospinal fluid from the brain to the pleural space, located between the lungs and the chest wall. This cavity, defined by the parietal and visceral pleura membranes, naturally contains a small amount of fluid [16]. Additionally, lumboperitoneal shunts (LPs) drain cerebrospinal fluid

(CSF) from the lower back to the abdomen, offering a less invasive extracranial option and providing another alternative for physicians [16].

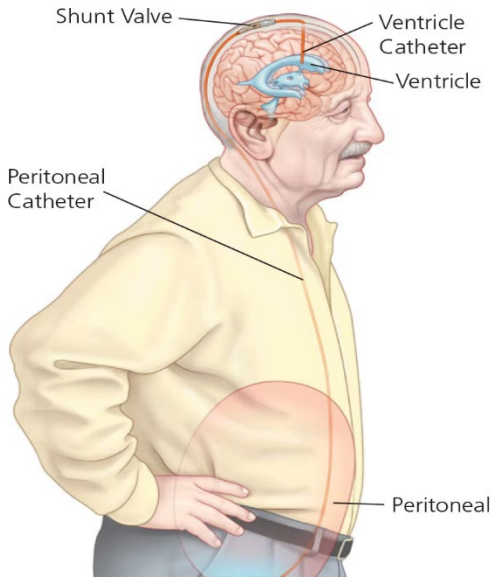

Figure 2 A graphic representing the components of a VP shunt [17]. CSF flows through the ventricle catheter, where it travels through the shunt valve and peritoneal catheter to a small opening in the abdominal lining, where it is absorbed.

Determining the number of people who have or have been diagnosed in the U.S is difficult, as NPH is an underdiagnosed disease. However, it is widely estimated that around 700,000 people currently have NPH in the U.S [3]. With only 20% of the estimated 700,000 NPH patients being diagnosed [3], we can estimate that there are 140,000 who are diagnosed with NPH living in the U.S at any given time. Determining the incidence of NPH is challenging, as there is limited information regarding the yearly diagnosis rate in the U.S. A study analyzing iNPH patients from 2008 to 2016 estimated the diagnostic incidence to be 2.86 per 100,000 [18].

Given that iNPH accounts for half of NPH patients and sNPH the other half, we can roughly double the 2.86 incidence rate to approximate that 5.5/100,000 is the total yearly diagnostic incidence rate of NPH. Given that there are approximately 340 million people in the U.S [20], we can extrapolate the incidence to estimate that 18,700 people a year are diagnosed with NPH in the U.S. This means that approximately 93,500 people a year develop NPH, with only 20% or 18,700 getting diagnosed. It should be noted that this estimate is of the entire population and that the incidence of NPH rises sharply with age.

1.3 Understanding Adelle Diagnostic's Technology

Adelle's primary goal as a neurodiagnostic company is to develop a platform that can predict the efficacy of shunt surgery for NPH patients, which would reduce unnecessary surgeries, as shunt surgery is not always an effective treatment for NPH. According to Levin et al. (2023), the research paper on which Adelle's technology is based, only 30% to 85% of shunt surgeries effectively treat NPH [2]. The founders estimate the success rate to be 50% based on their own research, meaning that approximately half of the shunt surgeries for NPH are ineffective. That said, the rate of shunt efficacy is highly variable. With a tool that can predict a potential shunt's effectiveness for a patient, the founders believe this would reduce unnecessary surgery while increasing the total number of NPH shunt surgeries, as patients who qualify would be less hesitant to undergo the procedure.

Levin et al. (2023) investigated the use of CSF analysis to predict the success of shunt surgery for NPH [2]. The study analyzed 42 patients and performed genome-wide RNA sequencing of extracellular vesicles in their CSF samples [2]. The researchers then identified specific biomarkers and pathways whose expression levels correlated with improvement in gait, urinary, and cognitive symptoms following shunt surgery [2]. The researchers then developed a

machine learning algorithm trained on these biomarker profiles that could predict if shunt surgery would lead to clinical outcomes with an accuracy of 80% [2]. The researchers identified specific biomarkers in cerebrospinal fluid (CSF) that correlate with symptom improvement after surgery and developed a machine learning algorithm to predict surgical outcomes. Adelle's founders aim to translate these research findings into the ShuntIQ test, a biomarker assay used in clinical practice to predict shunt surgery outcomes. Adelle plans to structure ShuntIQ as an LDT. In this model, a physician would administer the test and send the sample to a laboratory licensed by Adelle. This specialized lab would then perform the analysis using Adelle's proprietary DIMA system – a software tool integrating molecular and clinical data with machine learning to identify predictive molecular signatures. Upon completion of the analysis, the results would be sent back to the prescribing physician, indicating whether shunt surgery is recommended for the patient's NPH based on the ShuntIQ findings. In addition to their ability to predict shunt efficacy in properly diagnosed NPH patients, the founders of Adelle believe the ShuntIQ test holds promise for diagnosing and treating NPH in individuals exhibiting dementia-like symptoms but without an NPH diagnosis. Their reasoning stems from the observation that a significant portion of individuals with NPH are misdiagnosed, often being mistaken for having dementia. Consequently, they propose that CSF analysis using the ShuntIQ test could be applied to all dementia patients. They hypothesize that individuals identified by ShuntIQ as likely to benefit from shunt surgery are likely experiencing their dementia symptoms as a result of undiagnosed NPH. This hypothesis is supported by the fact that approximately five percent of dementia patients actually have NPH, and NPH is generally considered a substantially underdiagnosed condition [5].

LDTs are a type of in vitro diagnostic (IVD) test that is created, validated, and performed within a single laboratory [21]. These tests involve the collection, preparation, and examination of human body specimens, such as blood, saliva, or CSF, to measure various substances for health information [21]. The FDA regulates IVDs under the Federal Food, Drug, and Cosmetic Act (FFDCA) [22]. The FDA has historically exercised enforcement discretion for most LDTs, meaning premarket requirements were not typically enforced [22]. However, this approach is evolving, and the FDA has proposed a risk-based regulatory framework that would increase the oversight of LDTs to ensure their safety and effectiveness [23]. Adelle must successfully navigate the current regulatory frameworks if it wishes to get any test approved.

1.4 Other Neurodegenerative Diseases

While the founders of Adelle are primarily focused on NPH, they seek to potentially expand their diagnostic indications to other neurodegenerative diseases. Neurodegenerative diseases represent a diverse group of conditions characterized by the progressive loss of neurons, a process termed neurodegeneration [24]. This gradual deterioration of nerve cells ultimately leads to a decline in brain function, resulting in decreased mobility, coordination, strength, sensation, and cognitive abilities [26]. The prevalence of neurodegenerative diseases on a global scale is substantial, affecting millions of people [25]. Among these, AD stands out as the most common

type [25], but there are other common types of dementia, such as PD and Lewy body dementia (LBD), and vascular dementias [27].

The development of AD is associated with several core changes in the brain. The primary change is the accumulation of beta-amyloid protein outside neurons and the presence of twisted strands of tau protein within neurons [29]. Inflammation and brain tissue atrophy are observed as other alterations that occur during AD [29]. The accumulation of these plaques and tangles leads

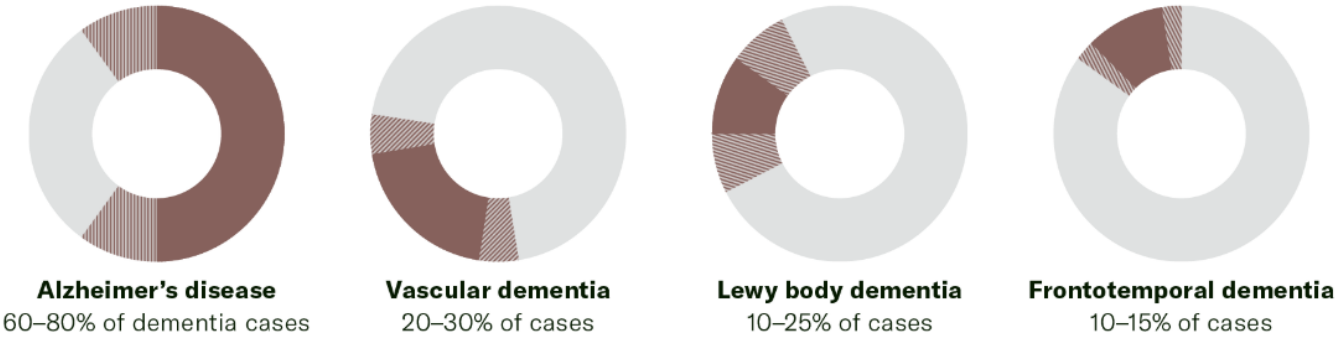

Figure 3: The estimated share of patients that each type of dementia has [28].

to damage and loss of connections between neurons, eventually resulting in neuronal death [30]. In the later stages of AD, a significant shrinkage of the brain (atrophy) is observed, resulting in severe cognitive decline [30].

AD and other variants of dementia are diagnosed by using a multi-faceted approach. This approach begins with a thorough clinical evaluation that encompasses medical and family history, symptom assessment, and a neurological examination to rule out other conditions [31]. Next, cognitive and functional assessments are conducted. These assessments include mental status tests and neuropsychological evaluations, which are crucial for determining cognitive decline and are often supplemented by family interviews [31]. Additionally, doctors use brain imaging techniques, such as MRIs, CT scans, and PET scans, to help visualize brain structure and function, while laboratory tests help exclude other potential medical causes. In recent years,

biomarkers have become increasingly vital in diagnosing AD, offering objective measures of underlying brain changes [32]. For instance, low levels of amyloid-beta measured in patient CSF samples often indicate brain plaque deposition, serving as an AD biomarker [33]. Researchers are also actively investigating blood-based biomarkers; tests are being developed to measure proteins like neurofilament light (NfL), which is elevated in AD and other dementias [32]. This rise of biomarkers presents a potential market opportunity for Adelle's platform, should the right technology be developed. However, many biomarkers currently used for AD and related dementias—such as amyloid-beta, tau, NfL, and GFAP—reflect general neurodegenerative processes rather than being disease-specific. Adelle aims to address this limitation by enabling the discovery of biomarkers more selectively associated with distinct neurological conditions, thereby offering greater diagnostic precision.

Current AD treatments primarily manage symptoms with medications like cholinesterase inhibitors and memantine [34]. However, there are emerging therapies that target the underlying pathology of AD, such as using monoclonal antibodies to target amyloid plaques [34]. Additionally, lifestyle changes, such as non-pharmacological intervention options, are becoming more common, including improving diet, exercise, and social engagement, which are crucial for supporting brain health and slowing cognitive decline. To maximize the effectiveness of these lifestyle changes, early intervention is crucial since interventions become less effective as symptoms progress [34].

PD is another common neurodegenerative disease characterized by the progressive loss of nerve cells in the brain. Specifically, the loss of the dopamine-producing neurons in the substantia nigra are responsible for the onset of PD [35]. The causes of people developing PD are somewhat unknown, but a combination of genetic and environmental factors is likely involved

[36]. The diagnosis of PD is primarily based on a clinical evaluation of symptoms, including tremors, rigidity, bradykinesia, postural instability, and a neurological examination [37]. Interestingly, the alpha-synuclein seed amplification assay in spinal fluid or skin shows promise as a diagnostic biomarker [38]. Lewy Body Dementia (LBD) is a similar condition to PD, as they both have a similar symptomatic profile. LBD is caused by abnormal deposits of alpha-synuclein protein (Lewy bodies) in the brain [39]. While the precise cause is unknown, it likely involves a combination of genetics, environment, and aging [40]. Diagnosing LBD is based on evaluating symptoms such as fluctuating cognition, visual hallucinations, tremors, and sleep disorders [41]. Similar to AD and PD, biomarkers from blood tests are also used to diagnose LBD [41]. LBD has no cure, but early intervention and certain antipsychotic medications have been shown to improve symptoms [42].

1.5 Understanding the NPH and neurodegenerative Biomarker Markets.

Given the widespread underdiagnosis of NPH, determining the size of the NPH diagnostic and surgery market is difficult. However, using our previous estimates of the diagnostic incidence and prevalence rates of NPH will allow us to get a preliminary understanding of how many people could benefit from Adelle's technology and what the market size for Adelle could be. To start, there are an estimated 36,000 shunt surgeries performed annually in the U.S., although this figure represents the total number of shunt surgeries, not just those for NPH [43]. While there is no available data on the yearly number of NPH shunt surgeries in the U.S., Adelle's founders believe the number is approximately 7,000 based on their research and expert interviews. With an estimated 18,700 patients diagnosed with NPH annually, the number of yearly shunt surgeries is likely slightly higher than 7,000. However, this number still provides a good starting point for a market sizing analysis. A 2019 report found the total cost of VP shunt

surgery to be approximately $131,000, highlighting the high expense of the procedure, including operative failure and other associated costs [44]. Therefore, we can estimate that the current yearly NPH shunt surgery market in the U.S is at least $917 million. Adelle's ShuntIQ test would be used to determine if shunt surgery is necessary and thus would likely be used by a greater number of patients than the 7,000 that receive shunt surgery. Using the estimated yearly NPH diagnostic incidence rate of 18,700, the market size for the ShuntIQ test system can be determined by multiplying the price of ShuntIQ by the number of patients. The founders have not yet set a price for ShuntIQ, but they anticipate a price range of $500-$1,500. Using $1,000 as the median price point, we can estimate that the total yearly potential market size for the ShuntIQ test is $18.7 million. Additionally, there are an estimated 140,000 people in the U.S currently diagnosed with NPH [3], meaning the total potential market size for the ShuntIQ test would be $140 million. While these numbers are high, it is unlikely that Adelle will capture a large share of this market in the first years following ShuntIQ's launch, as startups often take a relatively long time to acquire a sizable market share. However, the widespread underdiagnosis of NPH provides an opportunity for market growth should a higher share of NPH patients get correctly diagnosed. With 80% of Americans with NPH not being diagnosed with the condition [3], there is a great deal of room to grow in this market should the NPH diagnostic rate increase. Additionally, general trends in the U.S point to this market growing in the future. Since most people diagnosed with NPH are older than 60, the growth of the elderly population in the U.S, resulting from an increased median age over time, will likely lead to more NPH patients in the coming decades [5]. Additionally, the hydrocephalus shunt market, in general, is experiencing modest growth with an estimated current annual growth rate (CAGR) of 3.5% from 2024 to 2032 [45]. This is another indicator that there is a large and growing market potential for Adelle and

its technologies. Finally, estimates suggest the U.S. market for neurological biomarkers, valued at $2.74 billion in 2024, is anticipated to reach approximately $9.41 billion by 2034, reflecting a significant CAGR of 13.09% over that period [46]. This gigantic market would represent a very lucrative opportunity for Adelle should it be able to develop competitive technologies in this space.

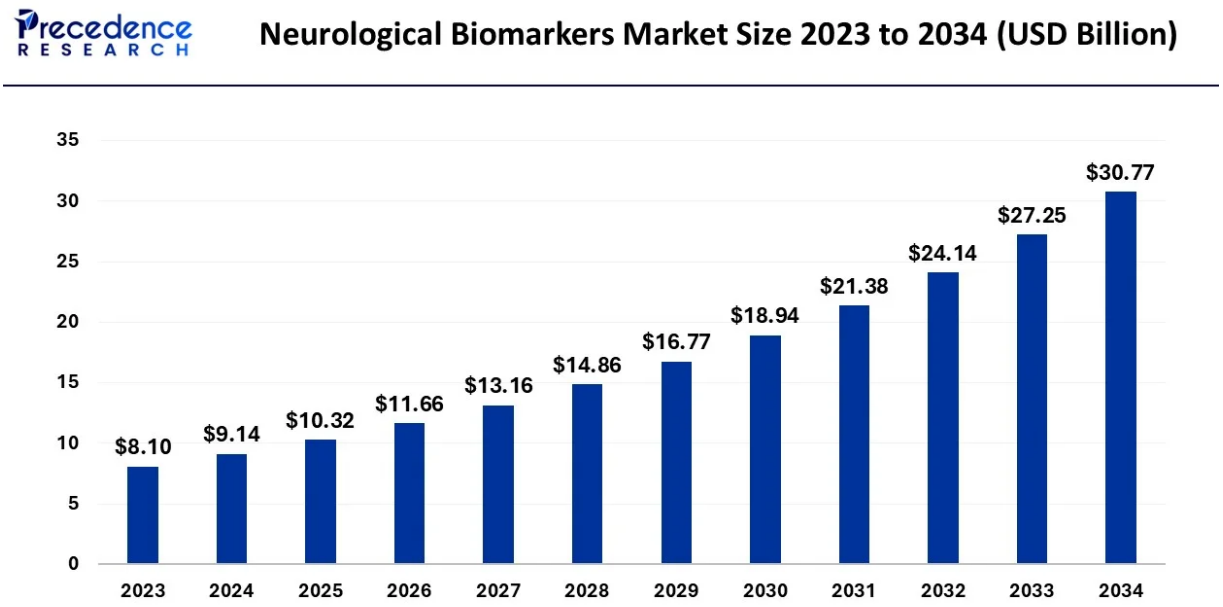

Figure 4: The projection of the global neurological biomarkers market from 2023 to 2024 as estimated by Precedence Research [46].

Chapter 2: Methods

2.1 The Competitive Analysis

A competitive analysis was conducted involving companies identified as potential competitors to Adelle Diagnostics. To ensure standardized data collection, the Pitchbook database, accessed via a Brown University subscription, served as the primary source for quantitative company metrics. Potential competitors were identified within Pitchbook by searching for specific keywords related to Adelle's focus, such as neurodegenerative diseases, or similar technologies, like biomarkers. An initial target of 90 companies was set for this analysis. However, one company was subsequently removed from the list as its information was deleted from Pitchbook after the initial selection, resulting in a final cohort of 89 companies analyzed. For each company, I researched and recorded the following data points from Pitchbook where available: current valuation, total capital raised, number of patents held, employee count, and annual revenue. In addition to Pitchbook data, I reviewed each company's official website to gather qualitative information about their core technology and market focus. My technology assessment specifically aimed to categorize each company based on its involvement in one or more predefined areas: 1) a focus on NPH, 2) utilization of CSF, 3) a focus on neurodegenerative diseases more broadly, 4) the use of biomarkers as a diagnostic tool, 5) the use of AI or ML, and 6) a focus on cancer.

Based on the alignment of their technology focus with Adelle Diagnostics' NPH-centric CSF analysis approach, I classified competitors as either direct or indirect. For example, a company primarily focused on oncology but utilizing biomarker analysis techniques similar to Adelle's approach would be classified as an indirect competitor, while a company developing a biomarker-based neurodiagnostic would be a direct competitor. Following data collection and

classification, I performed statistical analyses to identify potential trends. I calculated Pearson correlation coefficients to assess the relationship between measures of company success (valuation and total capital raised) and other variables, such as employee count and the number of patents. Furthermore, I employed linear regression analysis to investigate whether specific technological characteristics, such as a focus on biomarkers or the use of AI/ML, could serve as predictors of achieving higher valuations or securing greater amounts of capital. I omitted companies for which key data points (e.g., valuation) were unavailable on Pitchbook from these specific statistical tests to ensure the validity of the results.

My subsequent qualitative analysis focused on specific subsets of the competitor pool. I conducted an in-depth examination of five outlier companies characterized by exceptionally high valuations or total capital raised; this involved taking a closer look at their specific technologies and operational models to understand potential factors contributing to their market success. Similarly, I conducted a detailed review of the two companies identified as having an exclusive focus on NPH, given their status as the most direct competitors to Adelle Diagnostics. Finally, to evaluate the broader landscape and identify potential partners for Adelle, I analyzed 10 established biopharmaceutical corporations for their potential or existing involvement in the NPH diagnostics domain. These corporations included Medtronic, Roche, Johnson & Johnson, Abbott, Boston Scientific, GE Healthcare, Siemens Healthineers, Biogen, Novartis, and Eli Lilly. I gathered information regarding their relevant research and development activities, particularly concerning NPH diagnostics, from their company websites and other publicly available corporate information sources.

Company Name	Core Activities	Technology	Size	Stage of Development	Type of Competitor	Key Words	Sources
	A summary of the indications for which the company is working to develop products and the actions the company is taking.	The technologies the company is currently developing.	Valuation: Employees: Raised Capital: Patents: Revenue:	The stage of the clinical trials or marketing the startup is at for their device or treatment.	If the company is a direct or an indirect competitor to Adelle based on its device or treatment.	The words that the company used to describe their device or treatment which overlap with those that Adelle uses.	

Table 1: An example of the tables used to organize each company in the competitive analysis. Each section describes what information was added for the company.

2.2 Interviewing KOLs

To better understand the current landscape in which Adelle would be working, the founders of Adelle and I undertook a comprehensive qualitative investigation centered on KOLs and relevant stakeholders within the neurodegenerative disease space. The core objective driving this phase of our research was to gain a deep understanding of the current ecosystem surrounding the diagnosis of NPH and other neurodegenerative diseases, such as AD, with a particular focus on the challenges, unmet needs, and potential avenues for innovation. With Adelle seeking to develop a diagnostic tool for NPH and possibly other indications, our interviews sought crucial insights into the real-world problems faced by clinicians, researchers, and administrators in differentiating these conditions, the limitations of current diagnostic protocols, and the perceived readiness and requirements for adopting novel diagnostic tools like the one proposed by Adelle.

We aimed to uncover the specific pain points in the existing diagnostic pathway, gauge expert opinions on how the field might evolve, and understand what factors would drive the successful integration of a new technology aimed at improving diagnostic accuracy and patient outcomes, especially given that NPH is treatable but often missed or misdiagnosed as AD. Our approach was fundamentally guided by the principles we learned through the I-Corps training program, a methodology developed by the National Science Foundation to help researchers assess the translational potential of their inventions through direct market engagement. This framework emphasizes engaging directly with potential customers and stakeholders, not to pitch an idea but to listen and learn about their world, their problems, and their needs first-hand. Central to this was the concept of customer discovery, where the primary goal is to validate or invalidate key hypotheses about the market problem, the target customer segments, and the potential value proposition of a new technology. Rather than leading with Adelle's solution, we focused our interviews on understanding the interviewee's current reality. We formulated specific hypotheses before engaging with different stakeholder types; for example, we hypothesized about the frequency of NPH misdiagnosis, the challenges clinicians face in differentiating NPH from AD using current methods, the specific criteria hospitals use to evaluate and adopt new diagnostic protocols, and the underlying assumption that hospitals seek greater efficiency in dementia care. These hypotheses, derived from preliminary research and the project's premises, served as a guide for developing targeted, open-ended questions designed to elicit detailed responses and narrative accounts of the interviewees' experiences. To ensure a comprehensive perspective, we identified and recruited a diverse cohort of 26 individuals deeply embedded in the neurodegenerative disease field. This group included 14 neurologists and neurosurgeons, representing the primary clinical users and decision-makers directly involved in diagnosis and

treatment, four of whom are also actively involved in neurodegenerative research. We also interviewed four full-time neurodegenerative researchers to understand the scientific frontiers and biomarker landscape, three entrepreneurs working on related products to gain insights into the commercialization challenges, three patient advocates to incorporate the crucial patient perspective on diagnostic journeys and unmet needs, one Institutional Review Board (IRB) administrator to understand the regulatory and ethical hurdles for new clinical tools and research protocols, and one NPH patient to hear directly about the lived experience of the condition and the diagnostic process.

Identifying and securing interviews with these high-caliber individuals required a persistent and multi-faceted recruitment strategy. For interviews I conducted myself, I leveraged connections provided by the founders of Adelle, tapped into my own personal and professional networks built during my time at Brown University, utilized professional networking platforms like LinkedIn for targeted outreach, and engaged in direct cold calling and emailing. Securing these interviews, especially with individuals in specific administrative roles like billing and coding, was often challenging and required significant effort and perseverance. Each interview was approached as a structured conversation guided by our I-Corps training. The interview typically started broadly, asking about the individual's role, their typical day, and their general perspective on neurodegenerative disease diagnosis. We then delved into specifics, probing into the current diagnostic workflows they use or oversee, the explicit challenges and frustrations they encounter, the factors influencing their diagnostic and treatment decisions, and their vision for ideal future improvements. A significant portion of the interviews, particularly with clinicians and administrators, focused on the practicalities of adopting new technologies. We asked detailed questions about their institution's process for evaluating and integrating new protocols or

devices, including the specific criteria that must be met, common obstacles encountered, the key decision-makers involved in this process, and what ultimately motivates them or their institution to adopt innovations. We also asked for examples of past technological adoptions, both successful and unsuccessful, to learn from those experiences. Throughout this process, I meticulously documented the conversations, capturing key insights, direct quotes, and observations that supported or contradicted our initial hypotheses.

Upon completing the final interview, I analyzed the conversations, capturing key insights, direct quotes, and observations that related to our initial hypotheses and research questions. Following the data collection phase, I systematically processed the qualitative information gathered from all 26 interviews. Applying further techniques from the I-Corps methodology, I utilized their Customer Segment Profile framework as inspiration to help organize and structure the diverse inputs. This involved mapping the perspectives gathered onto components like defined customer segments, their articulated needs, potential value propositions, and the

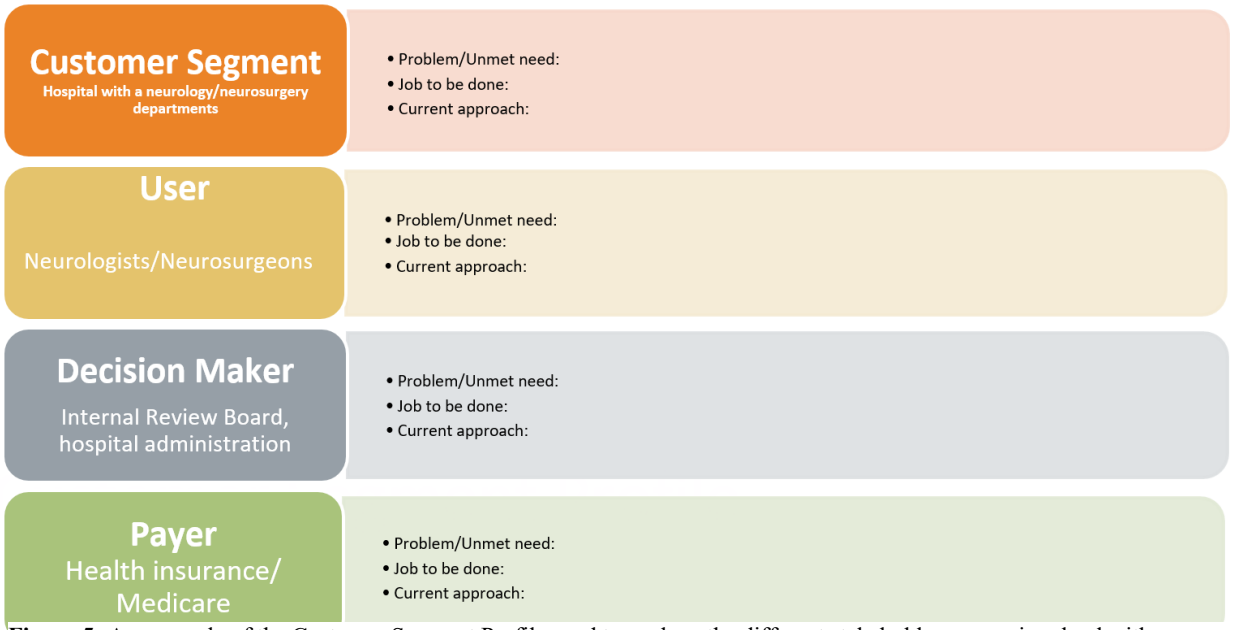

Figure 5: An example of the Customer Segment Profile used to analyze the different stakeholder groups involved with a neurodegenerative disease diagnostic test. This framework was filled out based on the key takeaways from each interview.

operational considerations discussed by interviewees. The process involved carefully reviewing interview notes and identifying recurring themes across different stakeholder groups.

Finally, I conducted a basic quantitative assessment of how frequently specific phrases were mentioned by each interviewee. These phrases included those regarding the potential of biomarkers, the use of AI or ML, the potential of blood-based or CSF biomarkers, the importance of early diagnosis, and the importance of predicting shunt efficacy. To compare the prevalence of these topics, bar graphs were generated for both the overall and NPH-focused analyses, showing the percentage of interviews in each set that mentioned the key phrases.

Chapter 3: Results

3.1 Competitive Analysis

In the competitive analysis portion of this research, I used Pitchbook to analyze 89 startup companies, including 50 direct competitors and 39 indirect competitors. I further researched 10 large and established biopharmaceutical companies. Each company was researched to determine its core activities and technologies to assess why these companies are (or are not) successful, how they are adding value to the biopharma industry with their proprietary technologies, and what strategies they are employing. The 89 smaller companies are all startups within the healthcare industry and are at different stages of growth, with some in the early stages of business development and others being publicly traded with large market capitalizations. The size and success of these companies were measured using a quantitative approach, which included the number of employees, the valuation, the number of patents, the revenue, and the funding these companies have. Each company was also assessed to see if it met the criteria for the following keywords that related to the platform that Adelle is developing. These keywords are Biomarkers, ML/AI, Neurodegenerative Diseases, NPH, and CSF. Other keywords for indirect competitors were also included, such as Cancer and Brain Imaging. Of these 89 companies, 59 focused on biomarkers, 37 on ML/AI, 64 on neurodegenerative diseases, three on NPH, six on CSF, and seven on cancer. The complete competitive analysis with sources can be found in **Appendix A**.

In our analysis of the 89 companies, we first wanted to see the relationship between quantitative measures and the company's success as measured by valuation and raised capital. The three quantitative measurements we assessed that were considered measurements of success were revenue, valuation, and raised capital, but we chose to measure valuation and raised capital

as the dependent variables in this study. We chose to do this because valuation and raised capital are reasonable measurements of success for all early-stage biopharma companies, many of which may be financially successful without generating any revenue. We believe that raised capital may be a better measure of company success, as the amount of money a start-up raises from investors objectively reflects how financially successful an early-stage startup is. In contrast, valuation can be a more subjective measure of a company's success, as its valuation is determined by a set of specific criteria evaluated by industry experts. Using both Adelle's direct and indirect competitors, we sought to determine if there would be a correlational relationship between our two measures of success and the number of employees or the number of patents the company has. To do this, we conducted Pearson correlation coefficient tests using MATLAB to determine if there is a positive relationship between these two variables. While we expected a positive correlation between revenue, raised capital, and valuation for direct and indirect competitors, we confirmed this fact and found that the correlation coefficient between all of these variables was greater than 0.7 and was statistically significant with a p-value less than 0.05.**Figures 6 and 7** show the correlation between the number of employees a company has and its valuation.

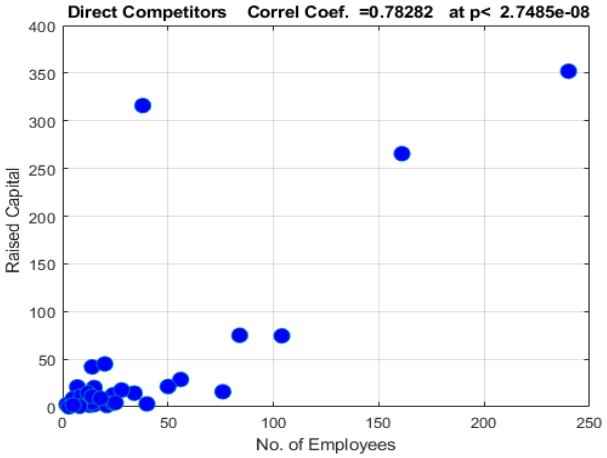

Figure 6: For Adelle's direct competitors, with a correlation coefficient of roughly 0.78, there is a strong and statistically significant (p-value < 0.05) correlation between the number of employees these companies have and the capital they have raised.

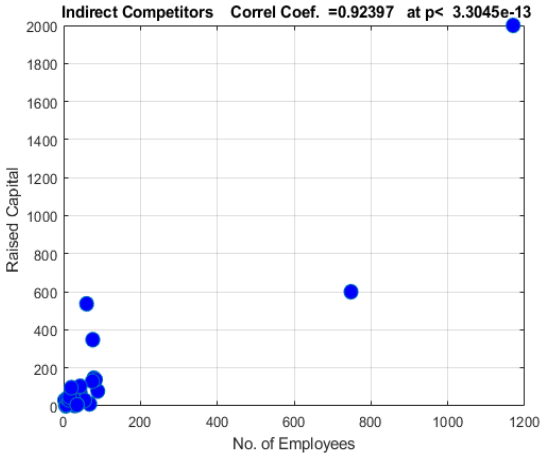

Figure 7: For Adelle's indirect competitors, with a correlation coefficient of roughly 0.92, there is a reasonably strong and statistically significant (p-value < 0.05) correlation between the number of employees these companies have and the capital they have raised.

Unsurprisingly, there is a positive correlation between the amount of money these companies have raised and their number of employees. With correlation coefficients of approximately 0.78 for direct competitors and 0.92 for indirect competitors, there is a strong and statistically significant correlation between these two variables. Next, we analyzed the relationship between valuation and the number of employees in **Figures 8 and 9**.

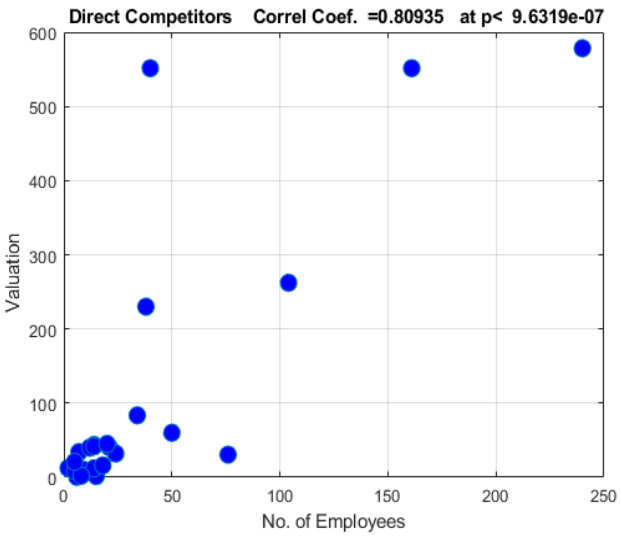

Figure 8: For Adelle's direct competitors, with a correlation coefficient of roughly 0.81, there is a statistically significant (p-value < 0.05) correlation between the number of employees these companies have and the valuation they have.

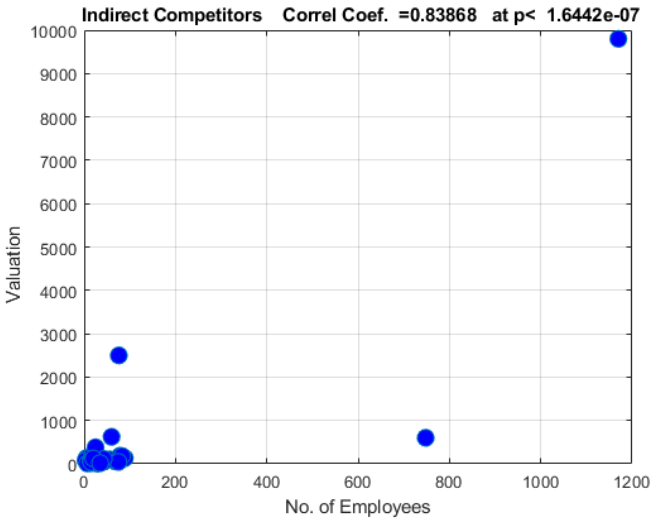

Figure 9: For Adelle's indirect competitors, with a correlation coefficient of roughly 0.84, there is a statistically significant (p-value < 0.05) correlation between the number of employees these companies have and the valuation they have.

We found similar strong correlations between these two variables in both direct and indirect competitors, with them having a statistically significant correlation coefficient of approximately 0.81 and 0.84, respectively. Given the relationship between raised capital and the number of employees, it was no surprise to find a similar relationship between employees and company valuations. While most of these companies are clustered in the bottom left corner of the figures near zero, there are outliers with much larger valuations and employees than the rest. We then sought to use the same Pearson correlation coefficient test to analyze the relationship between

how many patents these companies had and if that correlated with either raised capital or valuation. **Figures 10 and 11** show the relationship between patents and raised capital for direct and indirect competitors, respectively. Both direct and indirect competitors showed a strong correlation between the number of patents these companies have and the amount of money they were able to raise. **Figure 12** shows the relationship between patents and valuation for direct competitors, while **Figure 13** shows the same relationship for indirect competitors.

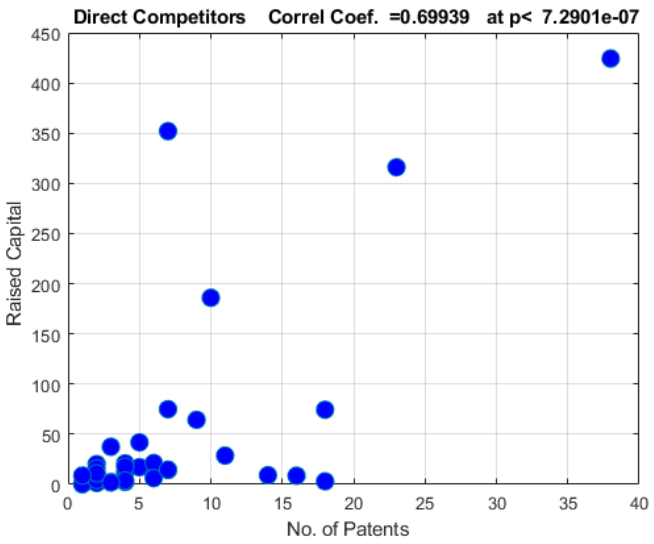

Figure 10: For Adelle's direct competitors, with a correlation coefficient of roughly 0.70, there is a statistically significant correlation between the number of patents these companies have and the capital they have raised.

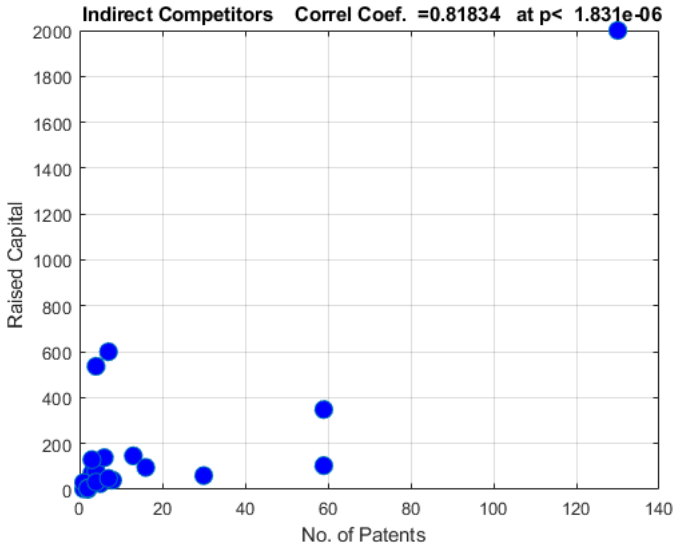

Figure 11: For Adelle's indirect competitors, with a correlation coefficient of roughly 0.82, there is a statistically significant correlation between the number of patents these companies have and the capital they have raised.

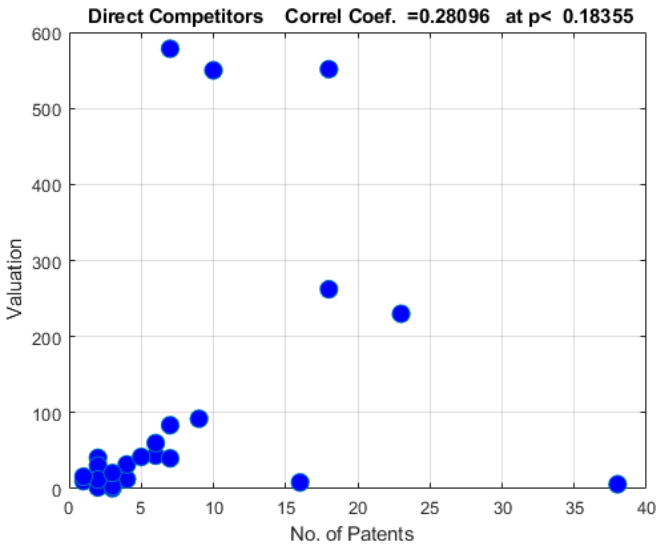

Figure 12: For Adelle's direct competitors, with a correlation coefficient of roughly 0.28, there is no statistically significant correlation between the number of patents these companies have and their valuation.

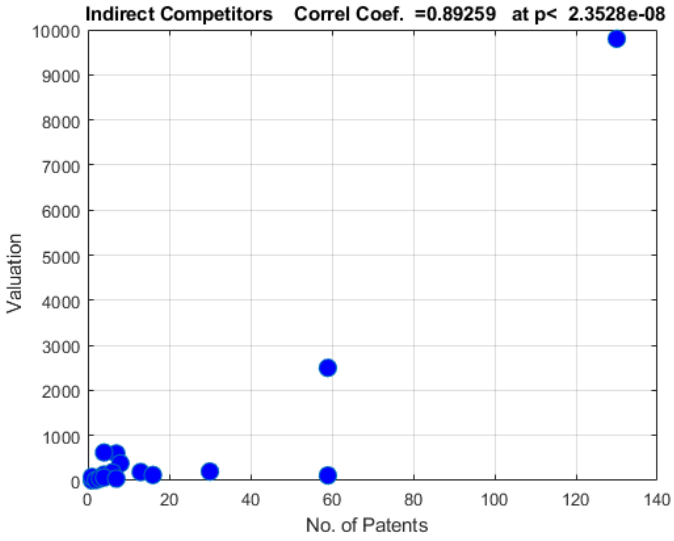

Figure 13: For Adelle's indirect competitors, with a correlation coefficient of roughly 0.89, there is a statistically significant correlation between the number of patents these companies have and their valuation.

When analyzing the patent-valuation correlations among direct and indirect competitors, a strong correlation emerged between patent quantity and the valuation of indirect competitors, whereas no such relationship was observed for direct competitors. This result differed from our analysis of raised capital and patent quantity, potentially showcasing a difference in how these variables can measure a startup's success.

To complement our initial analysis, we sought to conduct a more in-depth analysis to determine if there were relationships between success measurements and all variables measured in this study. To do this, we ran a generalized linear regression model to test the relationship between a company's valuation and the different variables used in this analysis (**Table 3).**

Predictors of Valuation				
Predictors	**Estimate**	**SE**	**tStat**	**pValue**
(Intercept)	**-384.72**	**267.97**	**-1.4357**	**0.16455**
No. of Employees	**8.8862**	**1.0079**	**8.8166**	**7.782e-09**
Revenue ($M)	**-19.39**	**3.2076**	**-6.045**	**3.6423e-06**
No. of Patents	**15.912**	**5.5993**	**2.8418**	**0.0092**
Competition 1 or 0	**-116.96**	**169.17**	**-0.69139**	**0.49624**
Focused on NPH	**-40.65**	**621.08**	**-0.06545**	**0.94838**
Focused on CSF	**121.54**	**449.48**	**0.27041**	**0.78926**
Focused on Neuro Degenerative Diseases	**199.81**	**240.18**	**0.83191**	**0.41401**
Focus Biomarkers	**76.222**	**212.31**	**0.35901**	**0.72286**
Machine Learning	**53.228**	**202.5**	**0.26286**	**0.795**
Focus on Cancer	**-258.66**	**302.19**	**-0.85595**	**0.40085**
34 observations, 23 error degrees of freedom **p-value = 1.63e-13**				

Table 2: A generalized linear regression model found that the number of employees, revenue, and patents that a company has are all strong predictors of their valuation based on a p-value < 0.05, as shown in the highlighted sections. The model found no other variables to be predictors.

We found that the number of employees, revenue, and patents a company has are strong predictors of the success of the company. These results align with the correlational analysis we conducted; however, using a linear regression model provides stronger evidence of this relationship. Interestingly, we found that the other variables did not predict the valuation of a company, suggesting that the type of technology that a company utilizes (such as focusing on biomarkers or using ML) may not be as important regarding a company's success when compared to how many patents the company has. We repeated this generalized linear regression

test to see which variables can predict raised capital in **Table 3**. We found that the results are similar to those of **Table 2**, where the number of employees, patents, and revenue are the only predictors of raised capital.

Predictors of Raised Capital				
Predictors	**Estimate**	**SE**	**tStat**	**pValue**
(Intercept)	**55.658**	**66.353**	**0.83882**	**0.40868**
No. of Employees	**1.6294**	**0.27735**	**5.875**	**2.5632e-06**
Revenue ($M)	**-2.0363**	**0.88776**	**-2.2937**	**0.02952**
No. of Patents	**2.881**	**1.5589**	**1.8482**	**0.045**
Competition 1 or 0	**-4.7383**	**44.783**	**-0.10581**	**0.91649**
Focused on NPH	**66.592**	**172.43**	**0.38621**	**0.70226**
Focused on CSF	**-27.325**	**123.75**	**-0.2208**	**0.82685**
Focused on Neuro Degenerative Diseases	**-32.262**	**55.204**	**-0.58442**	**0.56362**
Focus Biomarkers	**-22.175**	**54.372**	**-0.40785**	**0.68649**
Machine Learning	**-50.824**	**52.587**	**-0.96646**	**0.34209**
Focus on Cancer	**-22.116**	**80.903**	**-0.27336**	**0.78658**
39 observations, 28 error degrees of freedom **p-value = 2.11e-12**				

Table 3: A generalized linear regression model found that the number of employees, revenue, and patents that a company has are all strong predictors of their raised capital based on a p-value < 0.05 as shown in the highlighted sections based on a p-value < 0.05 as shown in the highlighted sections. The model found no other variables to be predictors.

The quantitative portion of our competitive analysis found that a company's number of employees and patents are strong predictors of its success. Our findings potentially mean that for

neurodiagnostic startups, the amount of intellectual property that the company controls may be the most important asset it has to secure capital and increase its valuation.

3.2 Analyzing Outliers in the Competition

To understand success factors in this competitive landscape, we analyzed outliers among our direct competitors, conducting a qualitative analysis of their operations to hypothesize their relative success. We researched their core activities and potential products to hypothesize why they might have been more successful. Overall, we found that companies with multiple products or technologies tend to have higher valuations and raised capital than those with only a single product. This finding aligns with our quantitative analysis, which revealed a correlation between patents and company success. More specifically, we found that companies developing both a drug and a companion diagnostic had the highest raised capital across the board. Given the pharmaceutical focus of the healthcare industry, small-molecule drugs with strong pre-clinical data have attracted significant investment, exceeding that of diagnostic-focused companies. The companies with both these promising drugs and companion diagnostics raised the most from investors compared to Adelle's other competitors, who developed diagnostics or treatments exclusively.

We then conducted an in-depth analysis of five companies in our quantitative analysis that had secured high funding and valuations to understand their ability to raise capital, increase valuations, and initiate clinical trials by examining their products and business models. The first company we homed in on was Cerecin Neurosciences. Cerecin is a healthcare company primarily focusing on developing treatments for a range of neurodegenerative diseases, most notably AD. Cerecin's lead asset, CER-0001, is an oral formulation of caprylic triglyceride used to induce ketosis to improve mitochondrial metabolism in the brain and is entering phase III

clinical trials [47]. CER-0001 is also being studied in two phase II trials that study it as a potential treatment for migraines and infantile spasms [48]. Cerecin is also developing CER-022, a radiolabeled tracer in the pre-clinical stage, and is being studied as a potential diagnostic for neurological diseases that have an underlying dysfunction in ketone metabolism, such as AD [48]. Cerecin's promising technologies that incorporate both a potential diagnostic and treatment for AD may explain why Cerecin has become a successful clinical-stage neurodiagnostic startup, boasting a valuation of $230 million, $317 million in raised capital, and 23 patents. The novel approach and pre-clinical success of Cerecin have seemed to differentiate it from its competitors, showcasing the potential importance of these attributes.

The following company we analyzed was Anavex Life Sciences. Anavex is a biopharmaceutical company that has developed Blarcamesine. This small-molecule drug can potentially treat different neurological conditions, including AD, Dementia, PD, and other less common disorders such as Rett syndrome [49]. Blarcamesine is being tested for these indications in multiple Phase II and III trials [49]. We had the pleasure of speaking to representatives from Anavex at the 2025 J.P. Morgan healthcare conference in San Francisco, who informed us that Anavex is conducting clinical trials in both the U.S. and Europe for AD treatments. Anavex also has three other drugs in pre-clinical development that focus on neurological conditions [49]. While Anavex is not working directly on a neurodiagnostic tool, it is conducting research that assesses how AI can detect biomarkers associated with Blarcamesine response in AD patients [50]. This signals the potential for Anavex to develop a companion diagnostic for its treatment in the future. With a market capitalization of over $600 million as a publicly traded company, it is clear that Anavex is a very successful startup with the potential to be even more successful should Blarcamesine be approved for clinical use. Our analysis of Anavex confirmed that

neurodegenerative drug developers are more successful than companies without drug development programs. Our analysis also showed that even a single drug in development could increase a company's valuation if it had multiple indications. In theory, each indication acts as an independent product, contributing to the overall value.

AC Immune is another clinical-stage biopharmaceutical company focusing on neurodegenerative diseases and has many products in its pipeline. AC Immune is developing treatments, diagnostics, and vaccines for neurodegenerative diseases associated with protein misfolding [51]. These neurodegenerative diseases include AD, PD, and other rare diseases [51]. The broad approach of AC Immune, whereby the company has different products for different indications in Phase III trials, again showcases how the companies with more products tend to raise more and be worth more. AC Immune boasts 107 patents and a market capitalization of over $200 million, proving that its diverse IP portfolio has allowed it to initiate the development of many products, increasing its value as a company significantly. Unfortunately, we could not find reliable data on how much AC Immune has raised, making us leave the company out of our quantitative analysis. Nevertheless, it is clear that through investments and partnerships with companies such as Takeda [52], AC Immune has the potential to raise billions of dollars and have many products approved.

The last two highly successful competitors from our quantitative analysis are Cassava Sciences and Alzheon. Both companies are successful clinical-stage biopharmaceutical startups creating drugs targeting AD. However, both companies are exhibiting noticeable drawbacks despite their relative success. Alzheon is developing two small-molecule drugs, with its primary drug, ALZ-801, being the only oral anti-amyloid treatment in Phase III testing for AD [53]. Alzheon also has a similar but potentially more potent drug in pre-clinical testing [53].

Interestingly, Alzheon is developing ALZ-801 for patients with two copies of the APOE4 gene as it aims to exhibit a personalized medical approach for its treatment [53]. This may indicate that Alzheon could create a companion diagnostic or partner with a company that has developed a genetic test for the APOE4 gene. That said, Alzheon is developing only two products with the same indication, which may limit its success should the Phase III trial not succeed. With a valuation of $550 million and $186 million raised, Alzheon can consider itself a successful startup for the time being. Cassava is a similar company to Alzheon as it is developing a small-molecule drug that targets AD, although they differ in that Cassava is also developing a companion diagnostic for its treatment [54]. Cassava's drug, Simufilam, restores the normal shape and function of altered filamin A [55], while its diagnostic tool, SavaDx, aims to detect AD with a blood test [56]. In October 2024, Cassava was considered a very successful company with a market capitalization of over $1.1 billion and a valuation of $788 million. Unfortunately, Cassava suffered a crash in its share price when Simufilam's Phase III trial failed [57]. As of January 2025, Cassava had a market cap of around $110 million and an enterprise value of around $5 million. To further Cassava's troubles, it is facing a class-action lawsuit that alleges that it misled investors regarding the expected efficacy of Simufilam [58]. Cassava's rapid decline highlights the risks for neurodegenerative startups with a single product in development. A diverse portfolio and a rigorous R&D operation can safeguard against the failure of one product, while tying a company's success to a single product means the company may fail if that product does.

3.3 Analyzing the Two Competitors Focused Exclusively on NPH

We also further analyzed Likvor and Rheaos, two companies developing NPH diagnostic tools similar to Adelle's technology, to compare their respective technologies with Adelle's and examine their funding and valuations. Likvor serves as Adelle's primary competitor as it has developed a technology with the potential to predict the efficacy of shunt surgery for NPH patients, which is the same indication Adelle is developing its ShuntIQ test for [59]. Likvor is an early-stage Swedish biotech company focused on assessing CSF dynamics. As of 2024, Likvor achieved $450,000 in revenue, $610,000 in assets, $2.59 million in valuation, and $2.42 million in money raised, an impressive statistical lineup for a company with six employers. From a financial standpoint, Likvor is more successful than Adelle as it has raised almost 10 times the money, although this is to be expected as Likvor was founded in 2007 while Adelle was founded in 2021, giving Likvor a sizeable head start [60]. Regarding Likvor's technology, it has developed a system named CELDA®, which assesses pre-operative and post-operative CSF dynamics to improve the diagnosis and treatment of NPH patients. The CELDA® system uses a machine learning system to assess CSF outflow resistance and other CSF dynamic parameters to determine the likelihood of a shunt being efficacious and how effectively the shunt performs after surgery. Currently, the CELDA® system is approved for clinical use in the European Union for diagnosing NPH and assessing CSF dynamics in patients [61]. It has not yet been approved for predicting the efficacy of shunt surgery in NPH patients in Europe and has not been approved by the FDA for any indication [62]. With three patents, EU regulatory approval, and decent funding for further research, it would appear as though the CELDA® system could be successfully implemented in two key areas of the NPH treatment pipeline. However, clinical trials studying the efficacy of the CELDA® system and similar CSF fluid dynamics to predict

pre-operative shunt efficacy in NPH patients have not been sufficient enough to warrant this system as a successful diagnostic tool for this indication in the U.S. A study [63] analyzed the CELDA® system's testing of CSF dynamics by injecting fluid in the lumbar and assessing the pulsatility curve for NPH patients. The presence of a Delta amplitude, which is the difference between the baseline pulse amplitude and constant phase amplitude of the pulsatility curve, was hypothesized to predict whether shunt surgery would be effective for NPH patients. The results of this study found that no correlation exists between Delta amplitude and shunt surgery outcomes [63]. Another study [64] found that using the CELDA® system to analyze a lumbar infusion test showed some promise in predicting the efficacy of shunt surgery for NPH patients, but its predictive power is still limited. Therefore, while Likvor presents as a clear competitor, there is enough reason to believe that if clinically successful, Adelle's biomarker-based diagnostic platform could outperform CELDA® for predicting shunt efficacy.

Rheaos is a competitor similar to Likvor as it is developing technology that aids in the treatment of NPH. Rheaos is developing its primary technology, FlowSense®, which is a thermal flow sensor that overlays a shunt to detect the presence of CSF [65]. This technology aims to assess the functionality of a shunt by monitoring the buildup of CSF in the patient to detect if the shunt has failed [65]. By focusing on NPH treatment, FlowSense® is not as close of a competitor to Adelle as the CELDA® system is since FlowSense® does not aim to assess how effective shunt surgery will be before it occurs. Nevertheless, by incorporating a system that uses prediction methods likely driven by AI [66], it is possible that, after approval, FlowSense® could be modified to either diagnose NPH or predict the efficacy of shunt surgery. With $12.7 million in funding and promising technology, it is possible that Rheaos may one day develop a non-invasive alternative to Adelle's technology.

3.4 Analyzing 10 Established Biopharmaceutical Companies

While the primary competitive analysis focused on startups and emerging companies, established biopharmaceutical corporations with potential NPH domain involvement were also examined, including Medtronic, Roche, Johnson & Johnson, Abbott, Boston Scientific, GE Healthcare, Siemens Healthineers, Biogen, Novartis, and Eli Lilly. Medtronic, a global medical technology company specializing in innovative medical devices and therapies for chronic diseases [67], demonstrates an established presence in NPH treatment through its development of shunts, despite not currently offering diagnostic tools [68]. This positioning suggests Medtronic as a potential strategic partner for NPH-focused companies like Adelle. Johnson & Johnson, possessing a robust medical device sector, presented a more ambiguous profile; while a 1995 acquisition of a shunt company occurred, subsequent divestiture for legal reasons obscured its current NPH involvement [69]. Boston Scientific, a leading global medical technology company, was found to be uninvolved in NPH diagnostics or treatment, though its engagement in neuromodulation devices suggests potential openness to other neurodegenerative indications [70]. Similar to Boston Scientific, GE Healthcare, while not currently active in NPH diagnostics, is investing in diagnostic tools for other neurodegenerative diseases, such as Alzheimer's disease [71]. Novartis, a global healthcare company focused on innovative medicines, also showed no current NPH involvement, although its extensive neurodegenerative disease treatment pipeline indicates a potential future pivot towards NPH [72]. Finally, our analysis revealed no discernible presence in the NPH space for Abbott, Roche, Siemens Healthineers, Biogen, or Eli Lilly.

3.5 Analysis of Interviews

To thoroughly understand the neurodegenerative clinical landscape, we interviewed 26 key opinion leaders whose diverse experiences shed light on the challenges in diagnosing and treating neurodegenerative diseases, particularly NPH. Our inquiry aimed to identify perceived shortcomings in the current system, explore potential improvements, and understand their expectations for the future of NPH and the broader field. The interviewees comprised a range of experts: 14 neurologists or neurosurgeons, four of whom also conducted neurodegenerative research; four full-time neurodegenerative researchers; three entrepreneurs developing related products; three patent advocates for neurodegenerative diseases; one IRB administrator and one NPH patient. A list of interviewees, each accompanied by bullet-point summaries of each interview, is provided in **Appendix B**.

While analyzing our interviews, we investigated how often specific key ideas and trends were mentioned. These ideas pertain to Adelle's potential diagnostic landscape regarding its ShuntIQ test and DIMA platform. The key ideas we looked for were the use of AI in neurodegenerative diagnostics, the use of biomarkers in neurodegenerative diagnostics, including blood-based biomarkers and CSF biomarkers (which is what the ShuntIQ test and DIMA platform uses), the importance of predicting shunt efficacy for NPH and the importance of early diagnosis for neurodegenerative diseases. The most common finding from our interviews was the desire for earlier diagnosis of neurodegenerative diseases. While treatment efficacy for neurodegenerative diseases varies between conditions, there is a consensus that earlier treatment will lead to better patient outcomes. Of the 26 people we interviewed, 21 emphasized the importance of early diagnosis, and of the 17 people who discussed NPH, 16 mentioned the importance of early diagnosis. Another significant finding from our interviews was that the

majority of those interviewed expressed either an expectation or desire for biomarkers to be used to diagnose neurodegenerative diseases, including NPH, AD, PD, and other dementias. These interviewees mentioned the potential for biomarkers to increase the ease and accuracy of neurodegenerative diagnostics while decreasing the cost and invasiveness of the diagnosis. Of the 26 people we interviewed, 16 mentioned the potential of biomarkers for improving diagnosis. 17 Interviewees specifically discussed NPH, of which 14 highlighted the potential use of biomarkers in improving diagnostic and treatment protocols. Some of those we interviewed emphasized the distinction between different biomarker collection methods. There was a common consensus that the least invasive ways to collect biomarkers were superior to other collection methods as they would be more cost-effective, easier to administer, and easier on the patient, increasing the likelihood of patient participation. While the ultimate ideal collection method would be saliva, there was a consensus that the best method most likely to be approved was blood-based biomarker diagnostics. Nine of the 16 people we interviewed who discussed biomarkers specifically mentioned their desire for blood-based diagnostic platforms. Notably, while seven out of the 16 people who mentioned biomarker use also discussed the potential use of CSF, all of these interviewees made it clear that a CSF platform was less desirable than other methods due to the invasive nature of a spinal tap that is needed to collect the CSF. However, certain interviewees speculated that while large-scale clinical trials for CSF-based diagnostics are generally improbable due to the invasive nature of lumbar punctures, trials evaluating biomarkers for predicting shunt efficacy in NPH patients could represent an exception, as these patients undergo lumbar punctures as part of standard care, thereby minimizing the incremental invasiveness of such a diagnostic.

We also analyzed our interviews to gain insight into how Adelle's ShuntIQ test would fare based on the opinions of our interviewees. Of the 17 interviewees who discussed NPH, 13 mentioned the value in predicting the efficacy of shunt surgery for patients. This finding indicates a clear need for a device like the ShuntIQ test within NPH healthcare, as neurologists, researchers, and advocates expressed this sentiment. Since the ShuntIQ test uses CSF biomarkers and the DIMA platform utilizes AI, we sought to determine how often these concepts regarding NPH were mentioned in our interviews. Of the 17 interviews, eight mentioned AI, and seven mentioned CSF when diagnosing NPH and predicting shunt surgery. This finding indicates that while there is interest in the specific mechanisms ShuntIQ and DIMA uses, there is a broader consensus regarding the importance of predicting the efficacy of shunt surgery. **Figure 14** and **Figure 15** provide a visualization of the percentage of interviews where these key topics were discussed.

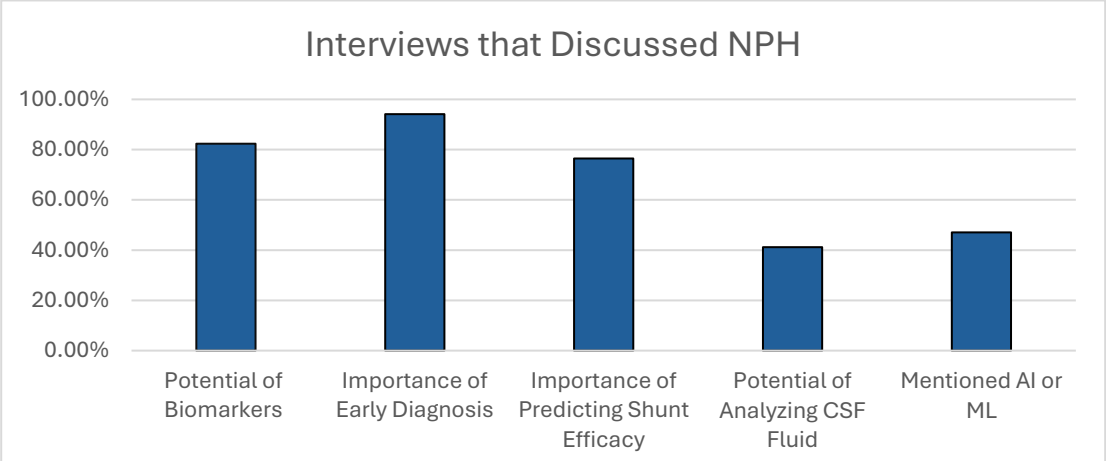

Figure 14: This bar graph shows the percentage of times each of these key topics was mentioned in the 17 interviews where NPH was discussed with key opinion leaders.

Our interviews found additional key trends and takeaways that provided a more robust insight into the current treatment landscape of neurodegenerative diseases. A significant finding regarding NPH was that there is a systemic lack of disease awareness that has impacted its diagnostic and treatment rates. Many physicians do not often consider NPH when being

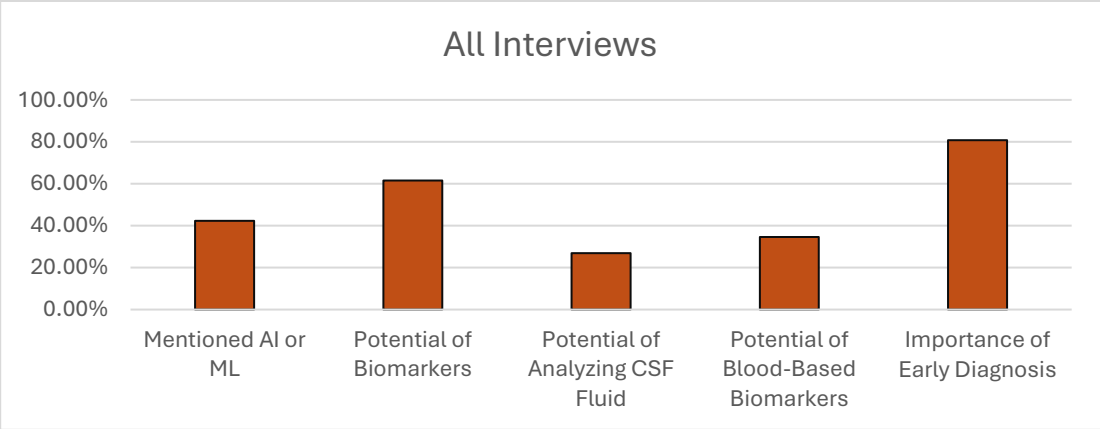

Figure 15: This bar graph shows the percentage of times each of these key topics were mentioned in the 26 interviews with key opinion leaders.

presented with a patient with symptoms, leading to chronic misdiagnosis and improper treatment. Patients and their loved ones are often unaware of NPH as a disease and may attribute symptoms to other conditions, such as urinary tract infections or arthritis. This lack of awareness can often delay the patient from visiting their doctor, allowing symptoms to get worse. Our interview with an NPH patient exemplified this issue, recounting a three-year delay in diagnosis due to an initial misdiagnosis of osteoporosis. This misdiagnosis resulted in a period of declining cognitive and motor function, coupled with unnecessary diagnostic testing. While the patient ultimately achieved a full recovery following shunt surgery, her experience underscores the critical need for heightened NPH awareness among both clinicians and the general public. We also found that physicians are willing to adopt new diagnostic systems if they are easy to use and have improved accuracy or other patient benefits. Physicians also emphasized that a robust safety profile and strong physician support are needed to convince a hospital to implement a new diagnostic

protocol. Hospitals also focus on cutting costs and having cutting-edge technology to compete with other hospitals. Therefore, we found that a new diagnostic system must be easy to use, inexpensive, and highly effective for it to be approved by a hospital's administration.

Chapter 4: Discussion

4.1 Takeaways and Implications from the Competitive Analysis

This research investigated the neurodiagnostic landscape to identify the characteristics necessary for a neurodiagnostic tool to maximize Adelle Diagnostics' financial success while remaining feasible within the company's current capabilities. The central hypothesis proposed that Adelle's most viable strategy involves developing a test specifically predicting shunt efficacy in NPH patients without pursuing other indications initially. It was further hypothesized that Adelle should prioritize securing robust IP protection for its test to enhance its value for potential licensing or sale. More specifically, the hypothesis suggested focusing the DIMA platform development on optimizing its effectiveness for predicting NPH shunt outcomes rather than adapting it for diagnosing other neurodegenerative diseases or disease outcomes. Beyond testing these hypotheses, the research also sought to determine additional characteristics required for a successful neurodiagnostic, considering current market conditions and stakeholder needs. Analyzing the research results yielded significant implications regarding the ideal attributes of such a product and highlighted areas requiring further investigation.

When analyzing the results from the competitive analysis, a major takeaway was the relationship between how many active patents a company had control of and the amount those companies are either worth or raised. For both direct and indirect competitors, there was a strong correlation between how many patents a company had and how much it was able to raise. This correlation was found using a Pearson correlation coefficient analysis and was confirmed using a linear regression model. Interestingly, while there was a strong correlation between the valuation and number of patents for indirect competitors, this relationship is not statistically significant for direct competitors. One potential reason for this lack of correlation was the small sample size

used for this particular analysis in which only 24 companies were analyzed since 26 of the direct competitors either had no data regarding their valuations or how many patents they have on Pitchbook. Another reason for the lack of correlation could be how valuations are determined and if a startup's valuation is the best measurement of its success. Valuating an early-stage startup is difficult, especially in the biotechnology industry, because traditional metrics like revenue, profits, or even established customer bases are often absent [73]. Risk-Adjusted Net Present Value (rNPV) is often used to value biotech and drug startups and is a valuation technique that estimates the current worth of a potential asset, like a drug candidate, by discounting its projected future cash flows according to the probability of successfully navigating each stage of development and approval [73]. Even though rNPV is calculated using objective measurements, valuation acts as a signal of market confidence and perceived potential, crucial for benchmarking and attracting resources, but may be subjective, volatile, and susceptible to market sentiment. Regardless of the reason for this lack of correlation, there is still a relationship between valuation and the number of patents based on the linear regression model, and it is clear that the IP strength a company has is a predictor of how financially successful it is in this research. Two primary themes may drive this relationship. Firstly, a larger IP portfolio can signal to investors a strong R&D capability, indicating the potential for multiple asset development or the application of a core asset across various indications. Within the neurodiagnostic industry, a company holding numerous patents might possess a diverse pipeline of technologies or drugs, increasing the likelihood of at least one achieving financial viability. Secondly, and perhaps more significantly, a substantial patent portfolio provides competitive advantages through enhanced market exclusivity and Freedom to Operate (FTO) for its technology. Enhanced market exclusivity can be achieved by patenting a broader concept rather than a specific technology,

which is facilitated by a diverse patent portfolio covering various functional aspects of the technology [74]. This limits competitors' access to the same market during the patent lifecycle, significantly boosting company value. Furthermore, FTO is crucial. Patenting a technology does not guarantee the legal right to use or develop it, as different entities might patent other components [75]. For instance, patenting a combination of technologies A and B does not confer FTO if the company lacks a patent for technology A alone. A robust IP portfolio is essential for securing FTO, enabling a company to develop and profit from its innovations [75]. These factors, among others, illustrate how a significant number of patents can contribute to the financial success of a neurodiagnostic startup. These results showcase the importance of a strong IP portfolio for Adelle. While Adelle currently has one patent application that covers the predictability of shunt outcomes using transcriptomics that are the basis of the ShuntIQ test, the company must file additional patents that cover every aspect of the ShuntIQ test and the DIMA platform, including the ML model, the workflow, and other mechanisms that are included in these technologies. Once Adelle has developed its technologies and achieved a greater understanding of its clinical value to the neurodiagnostic market, it must work to patent its ideas rather than its individual products. Adelle then must ensure that it has the FTO to use its technologies, which may require it to obtain the proper license(s) from the entities that hold the necessary patents to do so. By having a strong IP portfolio, Adelle would be in a strong position to attract investors who would value the limitations of Adelle’s competitors and Adelle’s ability to market its technologies as it would have the FTO to do so. Adelle would also be better positioned to license out the ShuntIQ test and DIMA platform to other companies if deemed a better option than to develop these technologies in-house.

Further insights arose from the qualitative analysis of high-performing outlier companies, identified by their valuations and capital raised. A consistent pattern among these successful companies was the presence of diversified product pipelines. Companies developing different products (or the same product for different indications) and possessing at least moderately successful clinical or preclinical data tended to exhibit higher valuations and greater capital raised. Notably, the most financially successful companies often possessed both a treatment option and a companion diagnostic. Key outliers such as Cerecin Neurosciences, Anavex Life Sciences, and AC Immune, each featuring varied pipelines targeting multiple neurological conditions for both treatment and diagnosis, underscore this principle. Offering innovations for both the diagnosis and treatment of a condition could grant a company access to two distinct markets, thereby increasing its overall value. This is compounded by the fact that an accurate diagnostic may lead to an increased diagnosis rate for a condition, meaning a company with both diagnostic and treatment capabilities could theoretically expand its treatment market, assuming the safety and efficacy of both are high. Following this logic, it is understandable that investors would view companies with both a diagnostic and a treatment favorably. Companies focused on a single diagnostic or treatment generally raised less capital and had lower valuations compared to those with multiple indications. However, companies developing therapeutics tended to achieve greater financial success than those focused on diagnostics. Several factors contribute to drug companies raising more capital, including the substantial costs and extended timelines associated with drug development [76]. Nevertheless, the significant revenue potential of a successful drug likely contributes to the higher overall valuation of companies with drug pipelines [76]. Based on this research, Adelle, having developed a single diagnostic tool thus far, would likely face greater challenges in achieving financial success compared to companies with

multiple indications. While developing additional diagnostics would be a prudent strategy, Adelle is currently engaged in such R&D, and its future success remains to be seen. Suggesting a shift toward drug or treatment development, such as an NPH shunt, is impractical given Adelle's dedicated resource allocation to molecular-based diagnostic R&D within the DIMA system. Nevertheless, Adelle has the potential to be a successful startup if it can leverage the principles identified in this competitive analysis that correlate with startup success. Likvor is the only company in this analysis that is developing a product with an identical indication as ShuntIQ, and it appears that Likvor's system is less accurate than Adelle's, giving Adelle a clear opportunity to develop [63]. Although Adelle cannot develop a shunt itself, exploring a partnership with a company that does, potentially positioning the ShuntIQ test as a companion diagnostic, could be beneficial. Regardless of its chosen path, this competitive analysis highlights the saturated and highly competitive nature of the neurodegenerative diagnostic market, underscoring the need for Adelle to be innovative in leveraging its technologies to differentiate itself from competitors, attract investors, and build valuation for long-term success.

4.2 Takeaways and Implications from the KOL Interviews

Interviews with KOLs provided insightful analysis and perspectives on the current diagnostic and treatment landscapes for both NPH and neurodegenerative diseases. The interviews were particularly informative regarding the existing challenges within the clinical management of these conditions, potential avenues for improvement, and anticipated changes in the coming years. These insights offered valuable context for understanding the challenges faced by Adelle and its potential for success as a startup in a highly competitive and saturated market.

A consistently highlighted theme across these interviews was the critical importance of early diagnosis for NPH and all other neurodegenerative diseases. Given that NPH is a treatable

condition, early diagnosis can mitigate morbidity by allowing affected individuals to receive shunt surgery without prolonged periods of misdiagnosis or treatment for other conditions while their symptoms worsen. Dorothy Sorlie, an NPH patient we interviewed, experienced a two-year progression of symptoms before receiving the correct NPH diagnosis. During this time, she lost her ability to swim and write, while her physicians initially suspected other conditions such as arthritis. The potential for early diagnosis of neurodegenerative diseases like AD to improve patient outcomes is more complex. A recurring point among interviewees was that early diagnosis of neurodegenerative diseases could facilitate lifestyle modifications that may improve a patient's morbidity and delay the onset of cognitive decline. Several physicians interviewed also emphasized that the efficacy of AD treatments like lecanemab is contingent upon administration before the occurrence of severe AD symptoms, aligning with findings in the scientific literature [77].

Kristen Cusato, the Director of Communications at the Alzheimer's Association Connecticut Chapter, expressed the belief that if AD could be diagnosed 20 years prior to symptom onset, lifestyle changes and treatments could significantly improve a patient's outcome. Conversely, other interviewees were less enthusiastic about diagnosing AD decades before symptoms manifest, expressing concern that it could cause individuals unnecessary distress knowing they would eventually succumb to an incurable or effectively treatable disease. These varying perspectives on early diagnosis underscore the need for improved diagnostics within the neurodegenerative landscape, a need likely recognized by investors. While Adelle has not yet developed a technology for formally diagnosing a condition, these sentiments highlight the potential market opportunity should it develop a test utilizing the DIMA system for NPH diagnosis. Regardless of this possibility, the overall investor attention on neurodegenerative

disease diagnostics could be advantageous for Adelle if sufficient private or public sector investment is directed toward this area.

Another significant theme highlighted in our interviews was the substantial underdiagnosis of NPH, preventing many affected individuals from receiving necessary care. This aligns with literature indicating that approximately 80% of NPH cases go undiagnosed [7]. Amanda Garzon, COO of the Hydrocephalus Association, attributed this systemic underdiagnosis to several factors, including the absence of a simple diagnostic tool, limited awareness of NPH, its varied clinical presentations, and skepticism about its existence among some physicians. Garzon believes a combination of improved diagnostics and increased awareness (the Hydrocephalus Association's primary aim) would lead to higher diagnosis rates. She also expressed optimism about the potential of genetic biomarkers in enhancing NPH diagnosis. Dr. Petra Klinge, a neurosurgeon at Warren Medical School at Brown University, echoed the need for novel diagnostic methods, noting the high cost of brain scans and suggesting a more accessible blood test as an ideal alternative. This widespread underdiagnosis of NPH presents both a challenge and an opportunity for Adelle. The limited diagnosis rate could restrict the potential user base for its ShuntIQ test, thus impacting revenue potential. Conversely, Adelle could strategically leverage this underdiagnosis. While developing a biomarker-based NPH diagnostic would offer the most direct financial benefit, Adelle could also partner with an organization like the Hydrocephalus Association to capitalize on increased awareness. If the Hydrocephalus Association successfully educates the public and physicians about NPH, it could lead to a higher diagnosis rate, even without immediate advancements in diagnostic technology. This increased awareness could then drive referrals to the ShuntIQ test, creating a mutually

beneficial relationship where the Hydrocephalus Association can offer a solution for NPH treatment to those they educate, and Adelle can benefit financially from increased test sales.

Analysis of KOLs' perspectives on the technologies and processes comprising Adelle's ShuntIQ test and DIMA system revealed a mixed sentiment regarding the utility and practicality of these systems and their potential implementation. Positively for Adelle, every interviewee who discussed NPH emphasized the importance of predicting the effectiveness of shunt surgery before it is conducted. Given that this is the primary indication that Adelle is developing its technologies, this confirms that Adelle is addressing a crucial unmet need in this landscape. Dr. Samantha Lanjewar, a Research Manager at the Hydrocephalus Association, highlighted the necessity for a more reliable method to predict shunt surgery success, as unnecessary surgeries can lead to various patient complications and even deter physicians from prescribing or patients from undergoing the procedure due to concerns about its efficacy. Dr. Lanjewar suggested that a CSF-based test for predicting shunt efficacy would be beneficial, while acknowledging that a blood-based test would be even more desirable. Dr. Abhay R. Moghekar, a neurologist at Johns Hopkins Hospital, also stated his opinion that a significant improvement in NPH care would be the ability to predict the effectiveness of shunt surgery beforehand. When questioned about the potential for an LDT predicting shunt efficacy to achieve sufficient kit sales to physicians, he indicated that it likely would.

While the widespread agreement that predicting shunt surgery efficacy would be clinically valuable is encouraging for Adelle, there are specific caveats regarding Adelle's planned test implementation and the KOLs' perspectives on what they believe will be useful or feasible. Every interviewee who discussed biomarker-based diagnostic tests emphasized the importance of non-invasiveness. Tests utilizing blood, saliva, or urine would likely see more

frequent adoption due to patients' greater willingness to undergo such procedures. Dr. Maria Dibner, a neurologist at Reliant Medical Group, anticipates that blood-based tests, the application of AI, and CSF analysis will become the gold standard for diagnosing neurodegenerative diseases in the future. Specifically addressing NPH, Dr. Dibner expressed hope that diagnosis could one day be achieved without a spinal tap, noting that her patients and their caregivers were very reluctant to undergo this procedure, a sentiment echoed by others.

Notably, every interviewee preferred noninvasive biomarker collection methods, and while some still believed that analyzing CSF could be a clinically useful tool for predicting shunt efficacy, others did not. Dr. Lauren Moo, a neurologist and professor at Harvard Medical School, believes that a large-scale clinical trial for an AD diagnostic that requires a CSF sample would be unlikely to happen as this would require asymptomatic patients to receive a spinal tap, a prospect that would make it very difficult recruit enough test subjects for this trial. Dr. Moo did state that a clinical trial relating to NPH could, at least in theory, involve the collection of CSF from patients since a surgical procedure on the patients' brain would happen regardless, since these patients would likely receive shunt surgery, as that is the standard of care for NPH. Dr. Moo still believes that a blood-based biomarker diagnostic would be the best testing method for a company wishing to commercialize an LDT that can predict shunt efficacy for NPH patients. Dr. Moo's belief that a clinical trial involving CSF collection is at least partially echoed by the other KOLs, who preferred other biomarker collection methods. This point of view would potentially make Adelle's plan to use the ShuntIQ test for all patients with suspected dementia symptoms very difficult. The founders of Adelle believe that since NPH is so underdiagnosed, a large number of people with dementia symptoms will have NPH and could benefit from shunt surgery, even if they have not been formally diagnosed with NPH. They estimate that 5-10% of dementia

patients have NPH, and this test could be used on all dementia patients to find the ones who benefit from shunt surgery. Based on these interviews, it seems very unlikely that the necessary clinical trial to approve ShuntIQ for all dementia patients would be approved by an IRB given its limited predictive potential (only 5-10% of those with dementia may have NPH [5]), difficulty in recruiting enough patients, and potential for complications. Since the ShuntIQ test is being designed specifically for NPH patients, it is likely that it would be approved as a test only for those who are already diagnosed with NPH. Dr. Garni Barkhoudarian, a neurosurgeon at the Pacific Neuroscience Institute, also addressed his skepticism of a test like ShuntIQ being used, even on NPH patients. Dr. Barkhoudarian stated that for his NPH patients, he will perform a lumbar puncture assay that drains 30 mL of CSF and can predict the efficacy of shunt surgery with about 70-80% accuracy. This would make his method of predicting shunt efficacy very similar to ShuntIQ regarding its testing procedure and the test's accuracy. An analysis of eight studies, however, showed that the accuracy of this test is closer to 62%, meaning ShuntIQ would be more accurate [78]. It is unknown how often neurosurgeons use this method. There are other attributes to this procedure for which ShuntIQ would improve upon, including the cost of the procedure being $1000-2000, whereas ShuntIQ would cost $500-1500, and the procedure requires the removal of 30 mL of CSF, according to Dr. Barkhoudarian. In comparison, the ShuntIQ test only requires 1 ml of CSF, according to Adelle's founders. Regardless of ShuntIQ's potential marginal benefit over this lumbar puncture assay, Dr. Barkhoudarian believes that there should be a better way to predict the efficacy of shunt surgery than to extract CSF. He also stated that the current accuracy of his test, being 70-80%, is not high enough and that he wishes a better predictive test could be developed. This opinion again does not bode well for the ShuntIQ test, which would have an accuracy of approximately 80% according to Adelle's founders.

In addition to these main takeaways, the KOLs also offered advice regarding the best practices necessary for successfully developing a neurodiagnostic tool. Allison Jean, a senior research review coordinator at Lifespan Hospital, outlined the crucial steps for a diagnostic tool to secure IRB approval for a clinical study. To obtain IRB approval, the scientific rationale underpinning the diagnostic tool must be strong and demonstrate a substantial benefit. A robust safety profile is also essential, with minimal likelihood of adverse effects for patients undergoing the test. Jean further emphasized that the study's primary investigator should possess strong credentials and be affiliated with the involved hospitals. Upon completion, the clinical study must provide compelling evidence of both safety and effectiveness for FDA approval. Furthermore, other KOLs underscored the importance of a low cost for a diagnostic system, as this enhances the likelihood of payor coverage. Given that payor coverage is vital for hospital reimbursement, a cost-effective diagnostic system is also crucial for hospital adoption. Physicians must also feel comfortable implementing and operating a new diagnostic system, implying that the test should be user-friendly and accompanied by adequate guidance. Beyond these factors, hospitals heavily rely on the endorsement of their physicians when deciding whether to adopt a new diagnostic system. Consequently, neurologists should be encouraged to utilize the system, which would also foster acceptance among other physicians who value their colleagues' opinions. Lastly, some KOLs noted the inherent challenges for startups to achieve success in both the neurodiagnostic and broader biotechnology markets. Based on these insights from the KOLs, to enhance its prospects of successfully developing and marketing an LDT, Adelle should strongly consider forming a strategic partnership with another company.

4.3 What Adelle Should Consider When Developing Its Diagnostic Tool

The central question guiding this thesis research concerned the characteristics necessary for Adelle Diagnostics' neurodiagnostic tool to achieve financial success. To address this, a dual approach was employed, combining a competitive analysis with insights from KOL interviews. This provided a holistic view of the current clinical landscape's needs and assessed how Adelle could best meet these needs given its technology and capabilities. I hypothesized that Adelle should focus on developing a diagnostic specifically for predicting NPH shunt efficacy, rather than pursuing other indications initially. Furthermore, I also hypothesized that Adelle should build a strong IP portfolio, potentially enabling future licensing opportunities. Analysis of the research results confirms the core validity of this initial hypothesis regarding Adelle's path to financial success, though it also reveals additional critical factors.

To enhance its likelihood of financial success, Adelle should continue developing its ShuntIQ test and DIMA system, albeit with key modifications to its current strategy. A significant drawback identified through KOL interviews is the ShuntIQ test's reliance on CSF collection for biomarker analysis. While developing a CSF-based test to predict shunt efficacy is feasible, its invasive nature, requiring a spinal tap, presents a considerable hurdle. This invasiveness could compound other potential shortcomings, possibly hindering commercial success. Gaining IRB approval for large-scale trials may be more difficult, as review boards might hesitate to approve a procedure perceived as causing more discomfort than alternatives. Even post-approval, physicians, patients, and their families might be reluctant to utilize a diagnostic test they deem invasive. Furthermore, similar procedures already exist where physicians drain CSF from NPH patients to gauge symptom improvement and predict shunt candidacy, such as the one mentioned by Dr. Barkhoudarian. Although the ShuntIQ test offers

potential advantages, such as requiring less CSF volume, it might only represent a marginal improvement over the existing practice.

Therefore, a strategic pivot towards developing ShuntIQ as a blood-based diagnostic appears advisable. A blood-based LDT would likely face fewer hurdles in approval and administration due to its less invasive nature. This shift could significantly increase the probability of successfully marketing the test, thereby improving Adelle's prospects for long-term financial success. KOL interviews clearly indicated a need for a reliable NPH shunt efficacy predictor, alongside a widespread interest in non-invasive biomarkers for neurodiagnostics – a trend echoed in the competitive analysis, which revealed numerous companies pursuing biomarker-based approaches. Consequently, a blood-based ShuntIQ test, if properly developed and implemented, holds substantial potential for commercial success. Encouragingly, Adelle is reportedly exploring whether its transcriptomic technology can be adapted from CSF to blood samples. This recommendation does not dismiss the potential commercial viability of a CSF-based diagnostic altogether; however, it underscores that a blood-based test likely offers a clearer path to widespread adoption and financial success, making it the more ideal target technology.

Beyond the sample type, Adelle must ensure its LDT possesses several key operational characteristics: ease of use, relative affordability, safety, and accuracy. The proposed price range of $500 to $1,500 seems potentially acceptable for payor coverage, but Adelle must conduct further research into payor willingness, particularly regarding the Centers for Medicare & Medicaid Services (CMS) reimbursement within this range. While a price range is considered, a functional prototype test has yet to be developed. During development, ensuring ease of use for physicians is paramount. Physician interviews revealed that while open to beneficial new

diagnostics, they require intuitive and easy-to-use systems to operate within their clinical practice. Since physician buy-in is crucial for hospital adoption, user-friendliness is essential.

Safety is another non-negotiable component. A strong safety profile is fundamental for both IRB study approval and eventual FDA clearance. Accuracy also requires careful consideration. While the current ShuntIQ test aims for approximately 80% accuracy in predicting shunt efficacy, this level may need improvement to be compellingly marketable. Estimates of baseline shunt effectiveness vary (founders suggest ~50%, some clinicians closer to 60%). Still, regardless of the precise figure, a more accurate predictive test would undoubtedly be more valuable to physicians and more commercially successful for Adelle. Thus, dedicating resources to research aimed at enhancing the accuracy of ShuntIQ, or any future diagnostic test, is crucial.

Findings from the competitive analysis strongly link a robust IP portfolio to the financial success of biopharmaceutical startups. Adelle should prioritize securing multiple patents covering various components of its diagnostic system(s). This strategy effectively patents the underlying concept or idea of the diagnostic system, not just a single iteration, which can significantly enhance its value to investors by limiting competition. This strengthened IP position could also facilitate future licensing or acquisition if deemed strategically advantageous. Moreover, a strong IP portfolio increases the likelihood of securing FTO, which is essential for legally marketing and selling the LDT diagnostic system.

Finally, Adelle should maintain a clear strategic focus on NPH, rather than diverting resources towards other neurodegenerative diseases at this stage. Although the founders envision expanding the DIMA platform to indications like AD or PD, and Adelle's website mentions broader neurodegenerative goals [1], the company currently lacks research, developed technology, and dedicated funding outside the NPH space. Attempting to enter the highly

saturated broader neurodegenerative diagnostic market, particularly for AD, would pit Adelle against immense competition, as shown in the competitive analysis. Conversely, the NPH diagnostic space has relatively few players, offering Adelle a clearer market opportunity.

This recommendation might seem counter to the competitive analysis finding that diversification (especially combining diagnostics and therapeutics) often leads to higher valuations. While that finding remains relevant for long-term strategy, Adelle's immediate constraints – limited resources, lack of non-NPH research, and a challenging funding environment – necessitate focus. As of April 2025, the biotechnology industry is experiencing a massive downturn, with investment drying up and investors becoming extremely cautious with where they choose to invest their money [79]. At the same time, there are cuts in funding to the National Institute of Health (NIH) and other federal agencies, reducing the likelihood of Adelle receiving federal funding in the near future [80]. Therefore, to best increase the likelihood of Adelle receiving investment, it should have a clear focus on developing a diagnostic for predicting shunt efficacy in NPH patients, an indication that Adelle has already developed the necessary technology for.

However, Adelle can strategically leverage the insights about diversification through partnerships. While developing therapeutics is impractical, Adelle could partner with an NPH shunt manufacturer, positioning ShuntIQ as a companion diagnostic offered alongside the shunt device. This could enhance the value proposition for both companies. Alternatively, partnering with a non-profit like the Hydrocephalus Association to increase NPH awareness could expand the market. As awareness and diagnosis rates rise, the Association could potentially recommend ShuntIQ testing, creating a mutually beneficial scenario: Adelle gains test volume, and the Association offers a tangible diagnostic solution to the community it serves.

In summary, the ideal diagnostic product for Adelle Diagnostics, shaped by its internal capabilities and the external pressures of the clinical and market landscape, is envisioned as a blood-based LDT accurately predicting NPH shunt surgery efficacy. To ensure physician adoption and payor acceptance, this test must be underpinned by a strong, defensible IP portfolio and developed with keen attention to usability, safety, and cost-effectiveness. By maintaining a disciplined focus on this core NPH indication while strategically exploring partnerships that leverage its technology, Adelle can navigate the current challenging biotech environment and build a foundation for future financial success and clinical impact.

4.4 Recommended Next Steps for Adelle.

With a clear understanding of the ideal diagnostic test, Adelle should map out the necessary steps to successfully market and develop it. Adelle's immediate priority should be to continue allocating resources to refine a blood-based test capable of predicting shunt surgery efficacy in NPH patients. Given the ongoing clinical study and related research at Brown University, Adelle is making progress toward this goal. Assuming Adelle successfully develops a blood test to predict shunt efficacy, it must ensure that the test's accuracy is at least comparable to that of the CSF test. However, as previously noted, the ShuntIQ test will likely require a prediction accuracy exceeding 80% to achieve commercial success. Therefore, Adelle must also prioritize enhancing the test's predictive accuracy.

Once the ShuntIQ test has undergone rigorous analytical validation, demonstrating adequate accuracy, sensitivity, and specificity, it must be certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) [81]. CLIA certification ensures the quality and reliability of laboratory testing. Following CLIA compliance, the test must be reviewed and approved by a hospital’s IRB before clinical trials can commence within that hospital. Upon trial

completion, the FDA may require Adelle to seek premarket approval for this LDT. However, due to ongoing litigation, the necessity of FDA premarket approval for LDTs remains uncertain [82]. Adelle must closely monitor evolving FDA regulatory practices to secure approval for its ShuntIQ test. Next, Adelle must obtain a Proprietary Laboratory Analysis (PLA) code for ShuntIQ [83]. This PLA code is essential for CMS and private insurance companies to price and reimburse ShuntIQ [83]. Ultimately, Adelle must secure CMS coverage for the ShuntIQ test, as CMS reimbursements will constitute a substantial portion of hospital revenues from ShuntIQ, given that Medicare covers the majority of individuals who would receive the test.

Beyond the development, refinement, and regulatory approval of ShuntIQ, Adelle must file a patent application and secure FTO to market the test. While patenting the underlying concept of the ShuntIQ test and the DIMA system is crucial, Adelle must ensure that the patent application meets the requirements for approval. According to 35 USC § 101, an invention must fall into one of four statutory categories to be eligible for patent protection: process, machine, manufacture, or composition of matter [84]. Abstract ideas, laws of nature, data structures, descriptive material, and electromagnetic signals are examples of concepts deemed ineligible for patenting as they are considered "basic tools of scientific and technological work" [84]. Consequently, Adelle must engage IP attorneys to ensure that its ShuntIQ patents are granted.

Once ShuntIQ is approved and Adelle has FTO, the company should explore strategies to maximize test sales. One option is to form partnerships with other companies, such as a shunt manufacturer, where ShuntIQ could serve as a companion diagnostic to the shunt. Adelle could also pursue a partnership with or acquisition by a large medical device company. Such a move could streamline the commercialization process, as larger companies typically possess the necessary financial resources and expertise. Alternatively, Adelle might partner with a company

specializing in NPH diagnostics, pooling resources to enhance the commercial prospects of both products. Likvor, with its financial capacity to bring an LDT to market and its existing NPH-related business model, could be an ideal partner. Although Likvor is developing a similar prediction test, its efficacy appears to be lower than ShuntIQ's [63]. Therefore, a partnership could be mutually advantageous, creating synergies that bolster the profitability of both companies. Regardless of its chosen path, Adelle should establish a partnership with the Hydrocephalus Association to broaden its network of physicians and treatment centers specializing in NPH, ultimately driving test kit sales and reaching more patients in need of improved shunt efficacy prediction.

4.5 The Limitations of This Research

This research, while providing a comprehensive analysis of the neurodegenerative diagnostic landscape and offering strategic recommendations for Adelle Diagnostics, is subject to several limitations that should be considered. The competitive analysis, though encompassing 89 competitors, could be expanded to include a greater number of companies for a more exhaustive market representation. Additionally, the depth of analysis for each competitor could be increased. A more in-depth competitor analysis would include details such as each competitor's burn rate, fundraising history, and information about their leadership team. Such an expansion would provide a more nuanced understanding of the competitive dynamics at play. Similarly, while the 26 KOL interviews yielded valuable insights, increasing the sample size would likely enhance the breadth and robustness of the qualitative data. A larger number of interviews may reveal a wider range of perspectives and experiences within the neurodegenerative disease space, potentially leading to more generalized conclusions. An inherent limitation lies in the potential for bias, which affects all research involving human subjects. In this study, the interviewees'

perspectives, particularly concerning the perceived invasiveness of procedures like spinal taps, may have been influenced by individual experiences and preconceived notions. This subjectivity could limit the objectivity of findings related to the acceptance of certain diagnostic methods.

Furthermore, the non-random selection of both competitors and interviewees introduces a risk of selection bias. The competitor selection was based on specific keywords and industry presence rather than a randomized approach, potentially skewing the analysis towards companies with higher visibility or specific technological focuses. The interviewee selection process, which relied on individuals agreeing to participate, may have overrepresented those with strong opinions or particular interests in the subject matter. This self-selection bias could limit the generalizability of the interview findings. Finally, the early-stage nature of Adelle Diagnostics presents a unique challenge. The lack of a fully developed prototype or a definitive business strategy makes it difficult to provide concrete directives regarding product development and commercialization. To navigate these limitations, Adelle Diagnostics should conduct further in-house research to refine its product development strategy and validate the findings of this analysis.

Chapter 5: Conclusion

This thesis investigated the optimal product development strategy for Adelle Diagnostics, a neurodiagnostic startup developing the ShuntIQ test to predict the efficacy of shunt surgery for NPH. Amidst a competitive neurodiagnostic landscape and a challenging funding environment, the central research question explored the essential characteristics required for Adelle's ShuntIQ test to achieve clinical adoption and financial success. Utilizing a mixed-methods approach combining quantitative competitive analysis of 89 peer startups with qualitative insights from KOL interviews, this research sought to validate or refine the initial hypothesis: that focusing

development on the NPH shunt prediction application, IP, and pursuing potential licensing offers represents the most viable path forward for Adelle.

The findings largely affirm the critical unmet need for a reliable method to predict NPH shunt efficacy, a procedure that is currently successful only about half the time. KOL interviews confirmed significant physician interest in such a tool. However, the research also highlighted significant hurdles and necessary refinements to Adelle's initial strategy. While ShuntIQ's CSF-based biomarker approach shows promise, KOLs expressed a strong preference for less invasive diagnostic methods, particularly blood-based assays, citing patient reluctance and procedural difficulties associated with lumbar punctures for CSF collection. Furthermore, the competitive analysis underscored the substantial financial advantages held by companies with robust, diverse IP portfolios and multiple product indications, revealing the inherent risks associated with single-asset diagnostic pipelines, especially in the current constrained funding climate.

Therefore, while the core hypothesis holds merit, the optimal path for Adelle requires strategic adaptation. The primary recommendation is to prioritize the development of ShuntIQ as a blood-based LDT, if technically feasible, leveraging the DIMA platform's capabilities while aligning with market preferences for non-invasiveness. Concurrently, Adelle must aggressively pursue broad and defensible IP protection covering not just the current test iteration but the underlying technological concept to build value and secure FTO. Achieving high predictive accuracy, potentially exceeding the initial 80% target, alongside demonstrating clear usability, safety, and cost-effectiveness, will be crucial for physician adoption and payor acceptance. Given market conditions and resource limitations, maintaining a strategic focus on the NPH indication, where Adelle has a technological head start and faces less competition, is advised over premature expansion into broader neurodegenerative markets. However, insights regarding

the value of diversification should be leveraged through strategic partnerships. Collaborating with shunt manufacturers to position ShuntIQ as a companion diagnostic or partnering with advocacy groups like the Hydrocephalus Association to increase NPH awareness and diagnosis rates could significantly expand market access and impact. **Figure 16** is a SWOT (Strengths, Weaknesses, Opportunities, and Threats) analysis summarizing the key findings of this thesis.

Figure 16: A SWOT analysis of Adelle and its ShuntIQ diagnostic test.

To conclude, while Adelle Diagnostics addresses a significant unmet clinical need within the NPH landscape, this landscape is relatively small given the rarity of NPH diagnosis, and the company's technology has limitations in effectiveness and scope that could make fundraising

difficult. Consequently, while clinically useful, ShuntIQ may not be a "blockbuster" diagnostic, and it is not possible to confidently predict Adelle's ultimate financial success. This thesis aimed not to guarantee profitability but rather to guide the founders in their efforts. Therefore, the recommended path forward—strategically pivoting towards a potentially blood-based assay, rigorously validating its performance, securing robust IP, maintaining focus on NPH, and actively cultivating partnerships—represents the most viable approach for Adelle to navigate the complexities of the neurodiagnostic market and position the ShuntIQ technology for its best chance at both clinical impact and financial success. Future efforts should refine the chosen assay format, enhance predictive accuracy, navigate the regulatory pathway, and execute a well-defined partnership strategy.

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Appendix A: Complete Competitive Analysis

Appendix B

The following is a list of the 26 KOLs interviewed for this thesis, accompanied by bullet points summarizing the key takeaways from each interview.

Legend: 1 = A neurologist or a neurosurgeon

2 = A Researcher of NPH or neurodegenerative diseases

3 = An Entrepreneur or products related to NPH or neurodegenerative diseases

4 = A patient advocate for NPH or Neurodegenerative Diseases

5 = A NPH patient

6 = An IRB Administrator

1. Dr. Marvin Sussman, PhD 2
    a. NPH needs to be diagnosed earlier and is often misdiagnosed as other diseases.
    b. There needs to be awareness about NPH for the public and healthcare providers.
    c. There is a need for accurate and non-invasive diagnostic tools.
2. Liz Dickman 3
    a. Diagnostic codes and device codes are very important for reimbursement.
    b. The CMS sets the standard price based on what they are willing to pay for treatments.
3. Dr. Deus Cielo, MD 1
    a. Lack of awareness about NPH makes it difficult to diagnose and treat.
    b. Lumbar puncture is a good predictor of shunt success, but it is invasive.
    c. A need for a non-invasive and rapid diagnostic tool for both NPH and shunt efficacy.
4. Joe Hofmeister 3
    a. Shunts may unpredictably clog, and there is a biological component to this.
    b. If there were a prediction method for shunt failure, that would be clinically meaningful.
5. William Butler, MD 1
    a. Early intervention and lifestyle modification are key.
    b. Socialization is good for neurodegenerative diseases.
    c. More precise diagnostics are needed.

6. Dr. Mark W. Albers, MD, PhD 1, 2
    a. There is skepticism about the existence of NPH and the benefits of shunt surgery.
    b. There needs to be a non-invasive way to test for NPH.
    c. A predictor of the success of shunt surgery.
    d. Incontinence is an early sign of NPH.

    e. Patients are hesitant about spinal taps, and a shunt-success predictor is necessary
    f. Identification of NPH through gait analysis is less invasive
7. Dr. Petra Klinge, MD 1
    a. Predicting shunt surgery success is very difficult
    b. A brain scan to diagnose NPH is too expensive for insurance. A blood test would be ideal if it existed
    c. A faster test is needed
    d. Can the same biomarkers be used for NPH diagnosis?
8. Steve Egan 3 NPH, Shunt E
    a. Has a company that has an adjustable valve for CSF
    b. Emphasizes the difficulty of the regulatory landscape
    c. Different shunt valves have different indications. Could different valves be used in relation to NPH diagnosis to maximize shunt benefit?
9. Dr. Rishi Lulla, MD 1 Biomarkers
    a. Treats pediatric patients with neuro-oncology problems.
    b. Talks about the drug approval pathway for cancer treatment but not much else
10. Dr. Francesco Ranieri 1 NPH, AI, Early diagnosis
    a. There are different imaging technologies, and the interpretation of them is complex
    b. There is a lack of awareness surrounding NPH, leading to delayed diagnosis
    c. To improve the diagnosis and treatment of neurological conditions through advanced imaging techniques, increased awareness, and collaborative efforts between healthcare professionals.
11. Dr. Gokalsan 1,2
    a. The IRB approval is needed to conduct research in a hospital setting
    b. Once a new treatment/diagnostic is approved, it must be covered by CMS, as they set the cost for the rest of the industry.
    c. He envisions more sophisticated tests, such as biomarkers, and how they could lead to early diagnosis.
    d. He stated that a hospital's desire to implement a new treatment is related to its cost savings
    e. The key is partnering with well-funded companies to avoid additional hospital costs and time, all contributing to the hospital's recognition as a cutting-edge institution.
12. Dr. Percy Griffin, PhD 2
    a. Testing neurodegenerative diseases with blood, urine, or saliva would be both cheaper and less invasive
    b. The ideal would be to detect early and slow down the progression of neurodegeneration
    c. Combination approaches will also be used in the future
13. Dr. Huey Interview, PhD 2
    a. He mainly does research on AD patients and not on other types

b. Mixed dementia is common and is often overlooked
c. Dementia treatment needs to be more specific
d. Combination therapy and measuring disease heterogeneity are the future.

14. Kaitlin Bennett Interview, 2
    a. Works on clinical research and IRB stuff.
    b. Strong preliminary data is needed for IRB approval.
    c. There is a lot of bureaucracy involved with research, but the institution wants to do research that it believes will advance science.
    d. There needs to be a physician buy-in for this research.
    e. More broadly, there needs to be more collaboration between the research side and the industry side. There also needs to be more of a focus on holistic health.

15. Dr. Prarthana Prakash, MD 1
    a. Works mainly on PD.
    b. Early intervention is NOT helpful for PD.
    c. New systems can be misused by doctors, but with proper training, this is not a concern.
    d. AI may be used in diagnosis, such as using gait speed and machine learning.
    e. The resources used are a factor in treatment for hospitals, but they mainly follow treatment guidelines.
16. Dr. Lauren Moo, MD 1,2
    a. Some physicians don't consider NPH a neurodegenerative disease.
    b. Adelle should focus on what it has that differentiates it from other companies.
    c. Adelle could focus on doing similar predictive tests for AD, but since there is no treatment, there is limited utility.
    d. The neurodegenerative space is very crowded, making success for a startup with limited publications very difficult.
    e. A large-scale CSF study will not happen for AD as there are asymptomatic patients, and those without symptoms will not want to have a spinal tap.
    f. A CSF study can be done with those who are already receiving shunt surgery. whereby the fluid can be tested and later compared to the outcomes of the patients
    g. If Adelle could predict the side effects of Alzheimer's Disease treatment, that would be clinically meaningful.
    h. Adelle needs a clear practical focus that can be funded and clinicians would want to use.

17. Allison Jean, IRB Administrator, 6
    a. To get IRB approval, researchers must be highly educated about the patients and potential risks to them
    b. The PI must have good credentials and be affiliated with the hospitals

    c. There must be a strong scientific backing to justify this research before it can be approved
18. Dr. Kara Smith, MD 1,2
    a. Early diagnosis is important for both NPH and AD, but super-early diagnosis is not helpful.
    b. A new diagnostic system has to go through the IRB, FDA, and be covered by insurance before it can be implemented.
    c. The benefits of switching to a new system must outweigh the risks and have sound ethics and science.
    d. There is a need for diagnostics that can use gait and AI to predict diagnosis. There is also a need for biomarkers taken from non-invasive sources such as saliva.
    e. The cost of the system is also a large factor.
19. Kristen Cusato 4
    a. AD is not normal aging, and people should be familiar with the signs of AD.
    b. Knowing that one will develop AD 20 years in advance can lead to lifestyle changes, which could improve the prognosis.
    c. Early testing and applications that can be used to understand disease progression and help to create a personalized medical approach would be very helpful.
20. Dr. Maria Dibner, MD 1
    a. Current AD treatments are not effective, limiting the efficacy of early AD diagnosis
    b. For NPH, early diagnosis is very helpful, unlike other neurodegenerative diseases.
    c. Early diagnosis of Lewy body dementia can be very helpful since the presentation is different than other dementias and hallucinations occur.
    d. A committee is in charge of adopting new systems, and they will do so at times.
    e. Technology should be easy to implement so that older doctors can do so
    f. She believes that the future holds blood-based tests, AI use, and CSF analysis to be the gold standard for diagnosing AD
    g. IF NPH could be diagnosed without lumbar puncture, that would be helpful.
21. Dr. Padraig O'Suilleabhain, MD 1
    a. PD can be better treated if found early, contradicting what Prarthana Prakash said
    b. New systems tend to be implemented as there is trust in the people that make these changes
    c. Financial challenges are the biggest
    d. Use of a new system is also contingent on whether other doctors use them
    e. There needs to be more technology on proteomics, transcriptomics, and other deep learning technologies that utilize bodily fluids
    f. In his hospital, patient outcome is the biggest factor that is considered
    g. For NPH patients, he does a gait and memory assessment to see if shunt surgery will be necessary, which is effective 50-75% of the time
22. Dr. Abhay Moghekar MD 1

a. Early intervention is key for AD but not for NPH, as the symptoms must progress to be treated
b. Drugs taken early may slow the onset of AD
c. Implementation of a new system depends on ease of use, scientific justification, and price
d. For NPH, better shunts and better prediction methods to select the right patients are both needed and expected to happen.

23. Samantha Lanjewar, PhD 2,4
    a. NPH is not well known and is often misdiagnosed as AD or PD.
    b. There needs to be a predictor for the eligibility of shunt surgery.
    c. Gait, cognitive decline, and urinary incontinence are the three main symptoms of NPH.
    d. She expects changes such as better imaging technology, smart shunts, and shunts that reduce infection, and new diagnostic tools such as AI and ML.
    e. Many researchers are looking into genes that could predict NPH.
    f. CSF biomarkers could indicate shunt efficacy, and there is research into blood-based biomarkers, but there is not yet good technology in this space.
24. Dorothy Sorlie 5
    a. NPH progression was slow and was initially misdiagnosed as osteoporosis.
    b. Symptoms progressed over 2 years; she couldn't sign her name or swim.
    c. She grew weaker and was gradually tested for other conditions that she did not have.
    d. She was told to consult a neurosurgeon, but not once was a CT scan performed.
    e. It took her almost three years to be diagnosed with NPH and receive surgery.
    f. She eventually made a full recovery a few years after surgery.
25. Amanda Garzon, 4
    a. The COO of the Hydrocephalus Association,
    b. The progression of NPH can be subtle; the three main symptoms are gait challenges, urinary issues, and cognitive decline.
    c. NPH is not well known, and symptoms are often addressed instead of the actual condition.
    d. There are issues related to treating NPH, including lack of belief in its existence, it is not a money maker, and doctors want quick fixes of which NPH has none.
    e. Wearables, AI apps, and home monitoring systems show promise for early detection of NPH and related conditions.
    f. Research on genetic markers and smart shunts could lead to better treatments.
    g. It is unknown why NPH is developed, but there is a potential genetic cause that biomarkers can find.
26. Dr. Garni Barkhoudarian, MD 1
    a. The sooner someone is treated for NPH, the quicker you can reduce their symptoms.

b. A lumbar puncture assay that drains 30mL of CSF can predict efficacy of shunt surgery to about 70-80%.
c. Shunt surgery works for NPH patients around 60% of the time.
d. The actual lumbar puncture procedure costs $1-2K.
e. Any new diagnostic or treatment system must be easy to implement and covered by CMS and private insurance.
f. In addition to FDA approval, a large retrospective trial would be necessary to assess the long-term efficacy of these new systems.
g. A prospective trial is the gold standard but these are difficult to conduct.
h. There needs to be a way to have a less invasive procedure than a spinal tap to predict the efficacy of shunt surgery.
i. A video assessment of Gait could also help predict the likelihood of someone with NPH vs. another disease.
j. If a patient is uninsured, the patient will not be treated with shunt surgery. This is an example where cost is essential since NPH is an outpatient workup. Luckily, most have Medicare.