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**Research Article**

# Snake Oil or Super Drug: How Have Regulators and Payers Perceived New Medicines that Target Asymptomatic Conditions?

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**Abstract**

**Context:** Assess how relevant precedent within the European Medicines Agency (EMA) (a key regulator) and the National Institute for Health and Care Excellence (NICE) (a key health technology assessment (HTA) body) can provide insights into how such novel medicines targeting asymptomatic conditions can be brought to market from both a regulatory and payer perspective.

**Methods:** All phase 2 or phase 3 clinical trials with keywords such as asymptomatic, pre-symptomatic, subclinical, premanifest, or preclinical keywords were downloaded from clinicaltrials.gov. Trials were cleaned to identify those for novel medicines with a primary focus on treating asymptomatic conditions. The EMA and NICE report for such drugs were downloaded online in December 2021 and analyzed to understand how they assessed the evidence.

**Results:** Two hundred seventy-eight clinical trials were identified. Of those, only 8 had relevant matching reports from the EMA or NICE, 7 received a positive review from the EMA, and 4 received a positive recommendation from the NICE. Those who received positive recommendations showed or were assumed to show statistically significant survival benefits given the short life expectancy of untreated patients.

**Conclusions:** There is no precedent within the EMA or NICE for approving or funding new medicines for asymptomatic patients where survival benefits cannot be established. Additional research is warranted to understand how regulatory and payer agencies can prepare for future generations of innovative medicines.

***Keywords***: Prevention, HTA, Regulatory, Endpoints

## 1. Context

There is limited literature discussing the challenges and solutions for regulatory bodies and payers with regard to treatments for asymptomatic patients. Bouvy et al. addressed this challenge, albeit with a narrow focus only on Alzheimer's disease (AD), rather than restricting the discussion solely to asymptomatic cases. As it pertains to asymptomatic cases, they simply concluded that there was a lack of valid and well-established outcome measures in this population and should be a priority for further explorations (1).

While treating asymptomatic disease is not necessarily new, the problems it will raise for regulators and payers warrant attention. This is due to the additional burden and complex challenges that can be expected from the diagnosis, treatment, and monitoring of such patients. It is important to gain a better understanding of these challenges and potential solutions because, without frameworks accommodating asymptomatic diseases, access to new medicines may be delayed or require larger, more expensive, and more complex trial designs (2).

On one end, diagnosing asymptomatic diseases is more complicated and likely to be more costly. Rather than relying solely on a differential diagnosis based on a discussion of symptoms between a practitioner and patient, testing is required. Doing so requires high quality and high precision since wrong diagnosis risks overtreating false positives or undertreating false negatives (3). This issue has a price, both in terms of the scientific innovation behind the test and the sheer volume, and will contribute to a rise in diagnosis costs that, by some estimates, are already around 10% of total healthcare expenditures (4). Furthermore, the availability of new medicines for asymptomatic patients could drive up demands for diagnosis, resulting in a larger pool of treatable patients than expected (5). This not only puts additional strain on healthcare budgets but also poses potential harm to patients: A Thailand screening package review decided against chest X-rays for the general population to detect

asymptomatic tuberculosis due to the possible harm caused by the diagnostic process (6).

The other end is related to the treatment and monitoring of such patients. Treatment efficacy is integrally linked to the ease of diagnosis: Diseases with a high diagnostic burden would inherently raise expectations for a therapy; otherwise, the steps to detect the disease may not be deemed worthwhile (3). There may also be concerns about paying for medicines that may not be taken as prescribed. One study on diabetic patients has found that some patients might discontinue their medication once they are asymptomatic as they feel they are cured or no longer in need of medicine (7). Finally, the treatment would likely come with a relatively high price tag, and an additional set of expenses can be anticipated concerning monitoring the patients to see if the treatment works or continues to provide benefits.

There are also novel ethical considerations when discussing treatment for asymptomatic patients. First, although a concerning fever, rash, headache, or other symptoms might universally prompt a discussion with a medical professional, it is only a more selective subset of patients who would actively seek or be subject to the detection of a disease for which there are no symptoms (5). Additionally, some pipeline treatments for asymptomatic disease have a target of delaying prevention; in these cases, where there are no current symptoms and the goal is to delay the onset of symptoms, how should a health technology assessment (HTA) body compare the cost-effectiveness of a pharmaceutical against potential lifestyle changes? In the example of AD, late- sequentially: First, the onset of symptoms can be delayed or prevented through lifestyle factors in place of medicine. Is it then worth spending potentially hundreds of thousands on medicine to prevent the onset of AD symptoms, or do you instead steer patients toward lifestyle changes at the risk of developing AD? (3)

Given these challenges, it is important to consider how a new medicine for an asymptomatic disease can be brought to the market. This typically involves two steps, including the regulatory assessment and the payer assessment, often conducted with input from HTA bodies. Normally, this happens sequentially: First, the regulator assesses the efficacy and safety of the medicine and makes a determination on whether it is safe and beneficial for use; the HTA would then add a cost-effectiveness lens to guide whether the medicine should be funded, and for which population, given limited healthcare resources. Therefore, it is important to consider the potential perspectives of regulatory bodies, such as the European Medicines Agency (EMA) in Europe, and HTAs, such as the National Institute for Health and Care Excellence (NICE) in the UK.

These may not be the same, though what is considered sufficient evidence for regulators may not meet the same hurdle for payers. For example, regulators often accept progression-free survival (PFS) as a primary endpoint in oncology trials and HbA1c in metabolic trials, but in a study of payer assessment in Germany, it was found that these endpoints were often deemed as not patient-relevant by the HTA (2). Currently, many HTAs, including NICE, give preference to medicines that address diseases with short life expectancy. This issue would consequentially disfavor many asymptomatic diseases, as it may be years before the progression of symptoms that relate to morbidity or mortality. Interestingly, studies have shown that this practice goes against public opinion: The general population would prefer to give more weight to medicines that improve quality of life rather than basing everything on mortality (8).

## 2. Methods

In order to look at available precedents, it was first necessary to identify drugs that have been studied in asymptomatic patients. Possible pharmaceuticals for use in asymptomatic patients were initially identified through a search conducted in December 2021 on www.clinicaltrials.gov. Two hundred seventy-eight phase 2 or phase 3 studies were found with keywords such as “asymptomatic”, “pre-symptomatic”, “subclinical”, “premanifest”, or “preclinical” in the condition search bar. Upon further review, some trials were subsequently excluded from the analysis, resulting in 180 clinical trials.

Further data were collected on the experimental drugs for each clinical trial. Where available, the experimental drug’s international non-proprietary name was found using www.adisinsight.com, which also provided information on the latest clinical development reported for each drug. Since some experimental drugs had multiple clinical trials (e.g., phase 2 and phase 3), 149 experimental drugs were searched. Through the information provided by www.adisinsight.com, 22 drugs were identified as having since been discontinued, and another 34 were identified as being pre-registrational (e.g., still in phase 2 or 3 and not yet registered with regulatory authorities). Some experimental drugs were studied multiple times but for different indications; at this stage, another 12 drug-indication pairs were excluded from analysis because they target brain metastases, which, while maybe asymptomatic, are generally not the primary focus of the medication under review (which target the underlying cancers). Ultimately, 101 unique drug-indication pairs were found.

To identify drugs that have received regulatory review, each of the 101 drug-indication pairs was searched via the online EMA medicine database. European Medicines Agency reviews were found for 29 drug-indication pairs, and the following files for each were downloaded for analysis: The European Public Assessment Report (EPAR) summary, a summary of product characteristics (SmPC), and a public assessment report. The files for one of these drug-pair indications (Rimonabant) were withdrawn but are still available. For another (aducanumab), there was only a “refusal of the marketing authorization” available,

which provided a rationale for the refusal.

To identify drugs that have received an appraisal from the NICE, the online NICE guidelines were searched and cross-referenced for each of the 101 remaining drug-indication pairs. NICE assessments were found for 17 drug-indication pairs, with another 11 in development and 2 being once available but have since been withdrawn.

For each drug-indication pair that had undergone an EMA review or NICE guidance (Figure 1), the clinical trial purpose, design, and results (where available) were analyzed and compared with the EMA review and NICE guidance resulting in identifying 8 drug-indication pairs that remained eligible for further analysis, as the others were identified as either not submitted to EMA/NICE or were not considered by EMA/NICE for one reason or another (for example, although the EMA or NICE may have published a report on the drug, it did not always assess the trial for asymptomatic patients as the study might have been exploratory in nature and therefore did not impact the registration/label).

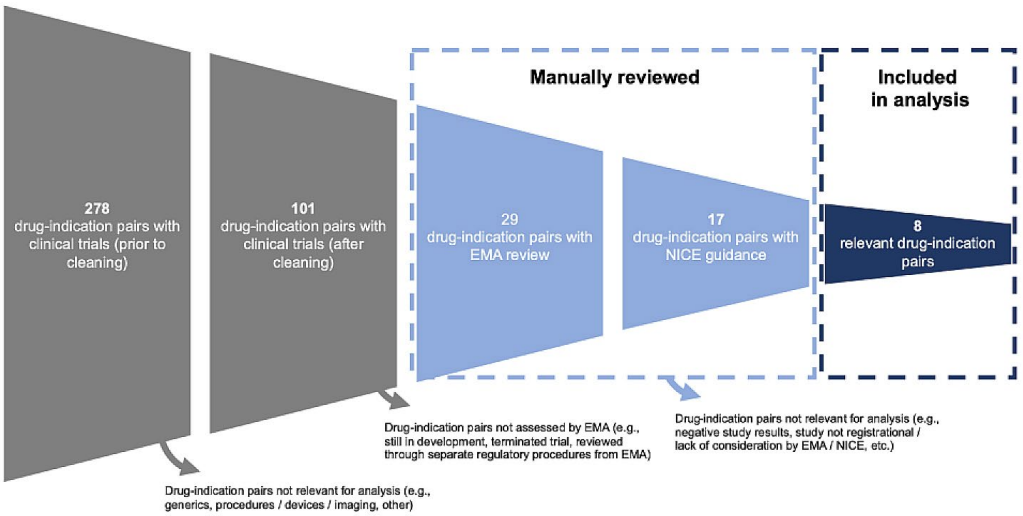


**Figure 1.** Scoping of drug-indication pairs for analysis. EMA, European Medicines Agency; NICE, National Institute for Health and Care Excellence.

## 3. Results

The clinical trials tend to be more recent (within the past decade): There were 61 trials with a start date in or after 2012, whereas only 40 had a start date before 2012. Only 38 trials were in phase 3 development (Table 1). There was also a heavy bias toward oncology: Over one in three (34 out of 101, 34%) were trials studying an oncology indication; another 26 were on infectious diseases (of which 5 were related to coronavirus disease 2019 [COVID-19]) (Table 1). Ultimately, eight drug-indication pairs met the criteria to be included in the analysis (Table 2). Results are summarized in Table 3. Following the table, additional details, as appropriate, are captured for each drug, providing context for the results.

**Table 1.** Summary of Clinical Trials Found

| | Of Trials |
|---|---|
| **Phase** | |
| Phase 1 / 2 | 10 |
| Phase 2 | 47 |
| Phase 2 / 3 | 6 |
| Phase 3 | 38 |
| **Indication area** | |
| Oncology | 34 |
| Infectious disease | 26 |
| Cardiology/vascular | 18 |
| CNS/neurology | 7 |

| | |
|---|---|
| Nephrology | 5 |
| Metabolic | 4 |
| Rheumatology | 3 |
| Gastrology | 1 |
| Ophthalmology | 1 |
| Healthy participants | 1 |
| Pain medicine | 1 |

Abbreviation: CNS, central nervous system.

**Table 2.** Drugs Included in the Analysis

| Analysis | Drug | Brand Name | Clinical Trial(s) | Indication |
|---|---|---|---|---|
| 1 | Abiraterone acetate | Zytiga® | NCT00887198, NCT01591122, NCT01867710, NCT04056754 | Prostate cancer |
| 2 | Artesunate/pyronaridine | Pyramax® | NCT03814616 | Malaria\|falciparum |
| 3 | Casirivimab/imdevimab | Ronapreve® | NCT04452318 | Healthy participants \| COVID-19 |
| 4 | Nusinersen | Spinraza® | NCT02386553 | Spinal muscular atrophy |
| 5 | Onasemnogene abeparvovec | Zolgensma® | NCT03505099 | Spinal muscular atrophy |
| 6 | Radium-223 chloride | Xofigo® | NCT02463799, NCT03002220, NCT02043678 | Prostate cancer |
| 7 | Risdiplam | Evrysdi® | NCT03779334 | Spinal muscular atrophy |
| 8 | Rituximab | MabThera® | NCT02320292, NCT00112931 | Lymphoma |

Abbreviation: COVID-19, coronavirus disease 2019.

**Table 3.** Summary of Results a

| Brand Name | Key Clinical Trial Assessed | Phase | Design | Stated Clinical Trial Purpose | Type of Diagnosis | Impact on Survival Measured? | Results of Study | Did EMA Grant Indication for Asymptomatic Patients? | Did NICE Recommend Treatment for Asymptomatic Patients? | Estimated ICER |
|---|---|---|---|---|---|---|---|---|---|---|
| **Zytiga®** | NCT00887198 | 3 | Randomized; double-blind; placebo-controlled | Efficacy | Biologic | Yes | Positive | Yes | Yes b | £28,600 and £32,800 per QALY gained |
| **Pyramax®** | NCT03814616 | 2 | Randomized; open-label | Efficacy | Biologic | No | Positive | Yes | Not available | N/A |
| **Ronapreve®** | NCT04452318 | 3 | Randomized; double-blind; placebo-controlled | Efficacy, safety | Biologic | No | Positive | Yes | No | N/A |
| **Spinraza®** | NCT02386553 | 2 | Open-label | Efficacy, safety | Genetic | Yes | Ongoing | Yes | Yes b | Not disclosed |
| **Zolgensma®** | NCT03505099 | 3 | Single arm; open-label | Efficacy, safety | Genetic | No | Ongoing | Yes | Yes b | Not disclosed |
| **Xofigo®** | NCT02463799 | 2 | Randomized; open-label | Efficacy | Biologic | No | Negative | No | No | N/A |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Evrysdi®** | NCT03779334 | 2 | Open-label; single arm | Efficacy | Genetic | No | Ongoing | Yes | Yes b | Above £50,000 |
| **MabThera®** | NCT00112931 | 3 | Randomized; open-label; versus watch and wait | Efficacy | Biologic | No | Positive | Yes | No | N/A |

Abbreviations: EMA, European Medicines Agency; NICE, National Institute for Health and Care Excellence; ICER, Institute for Clinical and Economic Review; QALY, quality-adjusted life year; N/A, not applicable.

[a] No population restrictions applied by the National Institute for Health and Care Excellence for recommended drugs.
[b] Managed entry agreement in place.

### *3.1. Abiraterone Acetate (Zytiga®) for Prostate Cancer, NCT00887198*

The EMA considered the context behind the therapeutic setting: Metastatic prostate cancer cannot be cured by the current therapy, median survival is usually less than 3 years, and most of these patients will die of their prostate cancer (9). Further, patients in this setting have, by definition, previously been diagnosed and treated for their prostate cancer, leaving no uncertainty on whether asymptomatic patients actually carry the disease.

The study results, as recognized by the SmPC, showed a doubling of radiological progression-free survival (rPFS) from 8 months in the placebo-controlled group to 16 months in the experimental arm (hazard ratio = 0.530, P-value < 0.0001). It also showed a significant increase in overall survival over 4 months, from 30.3 months to 34.7 months (hazard ratio = 0.806, P-value = 0.0033) (9).

The EMA and NICE were favorable in assessing this evidence; the clinical experts at NICE acknowledged Zytiga®›s benefit in delaying the progression of the disease and its potential benefit to overall survival, though it cautioned that the extent of this overall survival benefit was uncertain due to the elevated P-value (10).

### *3.2. Artesunate/Pyronaridine (Pyramax®) for Malaria | Falciparum, NCT03814616*

This study appears to have been designed in response to a request for more information from the EMA. The registrational study for Pyramax® had a fever as an inclusion criterion, so its efficacy was only proven in symptomatic patients. However, the EMA granted a non-restrictive label (11). As a follow-up, though, the committee requested that a post-approval study be conducted in asymptomatic patients (12).

The NICE did not assess Pyramax®, and, in fact, the EMA review was for its approved use outside of the European Union (EU). Therefore, no analysis of a cost-benefit assessment can be made.

### *3.3. Casirivimab/Imdevimab (Ronapreve®) for Healthy Participants | Coronavirus Disease 2019, NCT04452318*

The trial was positive, with a 31% risk reduction in developing symptoms (odds ratio = 0.54, P-value = 0.0380) (13). It submitted evidence to the EMA from this trial, among others, and requested a broad label, which the EMA largely granted (14).

Given the novelty and urgency of COVID-19, NICE did not issue a formal technology appraisal for Ronapreve® but instead provided a recommendation as part of its COVID-19: Rapid guideline (15). National Institute for Health and Care Excellence did not recommend the use of Ronapreve® in asymptomatic patients; in its review, it did not explicitly mention the study in asymptomatic patients, perhaps due to the newness of the study or limited capacity of NICE to consider all new information in a rapidly changing situation.

### *3.4. Nusinersen (Spinraza®) for Spinal Muscular Atrophy, NCT02386553*

The EMA assessment considered the interim results from this study with a median follow-up of 27 months (16). The report noted that all cases of spinal muscular atrophy (SMA) began with a pre-symptomatic phase, which is still detectable through genetic confirmation from birth. At the time of the EMA review, pre-symptomatic patients treated with Spinraza® were experiencing outcomes similar to children without SMA, creating optimism in the trial outcomes. The EMA said that the results corroborated the more established results in symptomatic patients and «support that early treatment, even prior to the onset of clinical symptoms, may be warranted for subjects with genetically diagnosed SMA» (16). It was also noted that patients treated in the pre-symptomatic phase had fewer adverse effects, suggesting a more favorable safety profile with early treatment. The writers of the report even speculated that, based on the interim results, “initiation of [Spinraza®] before the onset of clinical symptoms has the potential to delay or even prevent the progression of SMA disease and allow infants to develop normally» (16). Consequently, the EMA granted a broad label for all SMA patients.

The NICE was similarly supportive in its appraisal. The experts provided some caveat, though, saying that while there is some evidence of benefit in pre-symptomatic patients, there is no long-term evidence, so there is still a

high degree of uncertainty in the long-term, and further data would be necessary (17). Interestingly, the benefits in pre-symptomatic patients were not included in the economic analysis, and NICE hypothesized that the benefit would actually be higher in this population, so extending the use to this population could result in improved values. Ultimately, there was no Institute for Clinical and Economic Review (ICER) disclosed by NICE, but it did acknowledge that the product met the criteria for short life expectancy and overall survival improvement beyond 3 months. It should also be noted that the majority of SMA patients typically exhibit symptoms within the first 1 - 2 years of life, meaning that there is only a limited window for which pre-symptomatic treatment could be given.

### *3.5. Onasemnogene Abeparvovec (Zolgensma®) for Spinal Muscular Atrophy, NCT03505099*

While the EMA only had the interim results from this study available for its assessment and acknowledged that the results were inconclusive and too early to draw any conclusions, it took an optimistic approach and granted a broad label that included pre-symptomatic patients, similar to that of Spinraza® (18). The EMA requested the manufacturer to submit the final results from its study in order to confirm the efficacy and safety in this population.

The NICE was similarly optimistic, recommending the use of Zolgensma® for pre-symptomatic patients in its guidance (19). Despite the absence of clinical trial evidence, the clinical experts cited a yet-to-be-confirmed theory supporting the rationale for why Zolgensma® is expected to work better in pre-symptomatic patients. The NICE has cited two key contextual factors in its guidance: First, pre-symptomatic patients are diagnosed genetically, and second, this population may currently be treated with Spinraza®. It has also been acknowledged that a very small number (~2) of pre-symptomatic SMA patients are diagnosed in England each year (19).

### *3.6. Radium-223 Chloride (Xofigo®) for Prostate Cancer, NCT02463799*

An interim analysis of this study showed a higher risk of bone fracture and a trend for increased mortality in the Xofigo® arm, and the study was terminated early. Therefore, the EMA ruled that Xofigo® is contraindicated for this use and specified in its indication statement that it is for symptomatic patients only (20).

### *3.7. Risdiplam (Evrysdi®) for Spinal Muscular Atrophy, NCT03779334*

This is a very recent trial, and no results were considered part of the EMA assessment. However, the EMA did not restrict the label to symptomatic patients, leaving it open to interpretation (21).

While the EMA did not explicitly mention pre-symptomatic patients, the NICE did: They are included as part of the recommended use in England, so long as the conditions of the managed access agreement are followed (22). Based on interim results from the trial in which 5 patients were assessed who had been using Evrysdi® for at least 12 months, the NICE committee cited «some evidence» that Evrysdi® worked in pre-symptomatic patients. The committee was surprisingly flexible by NICE›s standards (22). Like with Spinraza® and Zolgensma®, cost-effectiveness information for pre-symptomatic patients was not shown, and the NICE estimated an ICER above £50,000.

### *3.8. Rituximab (MabThera®) for Lymphoma, NCT00112931*

Despite the study results being published and the endpoint achieved, the EMA did not appear to consider this evidence in its review. It makes no mention of the trial nor discusses when treatment should be initiated with regard to the onset of symptoms (23).

Conversely, the NICE restricts the use in England to only those with symptomatic stage III and IV follicular lymphoma in previously untreated patients (24). The NICE does not discuss the results of this trial, so it cannot be determined how they considered the evidence, if at all. However, it should be noted that the primary endpoint does not inform morbidity or mortality, which is generally required of HTAs, and no survival benefits were shown.

## 4. Discussion

Five observations, discussed below, can be made following the analysing of the results.

### *4.1. Observation 1: While There Is Very Little Precedent for Treating Asymptomatic Patients, Interest Appears to Be on an Upward Trajectory*

The concept of asymptomatic or pre-symptomatic treatment appears to be a new one. Clinicaltrials.gov has 102,983 phase 2 or phase 3 studies in its database; only 278 (0.3%) of these studies were conducted under an asymptomatic condition (25). The majority of these trials have started in the past 10 years, and only 8 of these trials provide some sort of precedent for how the EMA and NICE would weigh this evidence from a regulatory and HTA point of view, respectively. This suggests a trend toward more interest in treating asymptomatic conditions and a potential need for new frameworks to assess the value of drugs in these indications.

### *4.2. Observation 2: There Appear to be Unwritten and Inconsistent Rules Applied to Asymptomatic Conditions*

Unwritten rules seem to exist and vary based on where the condition/drug fits along two dimensions: (1) whether or not the underlying condition leads to mortality or

morbidity; and (2) whether or not the treatment has a halo effect. This can be mapped in a two-by-two framework that identifies four quadrants of asymptomatic disease (Figure 2):

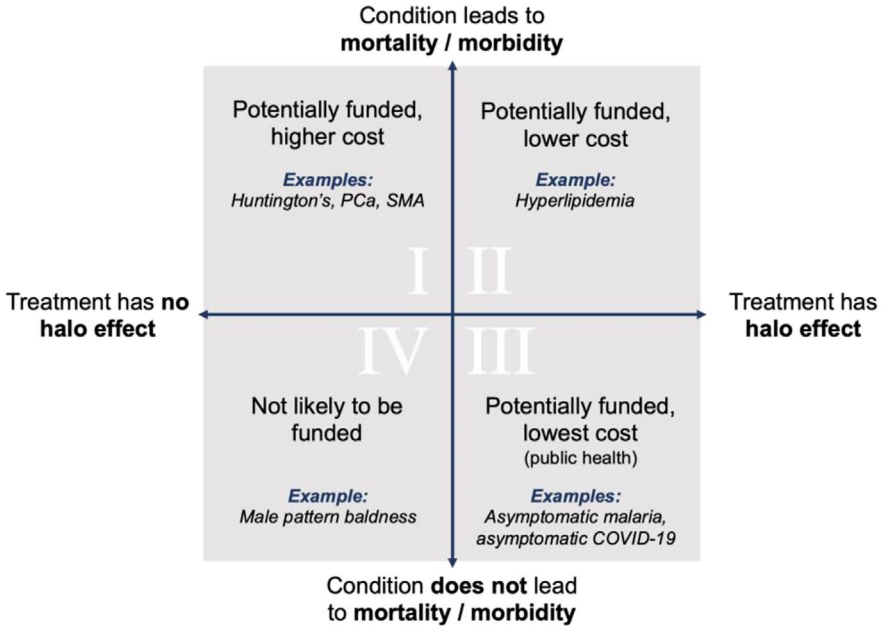


**Figure 2.** Asymptomatic disease quadrants. PCa, posterior cortical atrophy; SMA, spinal muscular atrophy; COVID-19, coronavirus disease 2019.

- Quadrant I | the condition leads to mortality/morbidity, but there is no halo effect from treatment. Many of the cases in this paper's analysis fall into this category (e.g., SMA and prostate cancer). There is also the potential for high reimbursement prices for these drugs since the cause-and-effect is potentially clear between treatment and the impact on mortality/morbidity. Here, traditional frameworks have been applied, and the approved treatments have benefited from being able to show survival due to short life expectancies.

- Quadrant II | the condition leads to mortality/morbidity, and there is a halo effect from treatment. An example here is hyperlipidaemia, which, interestingly, did not show up in this paper's analysis of asymptomatic treatments. While hyperlipidaemia is asymptomatic, it has been shown to lead to morbidity and even mortality through its correlation with other conditions. It is the impact on these other conditions, such as stroke, that was ultimately of interest to regulators and payers (26). Since the link between the drug and the treatment effect is less direct, there may be more uncertainty for medicines in this quadrant and potentially a lower cost negotiated. Indeed, as there became less confidence that Aduhelm® impacted AD progression and the only sure benefit was its potential impact on amyloid plaque accumulation, Biogen decreased Aduhelm®›s list price in the US by 50% (27).

- Quadrant III | the condition does not lead to mortality/morbidity, but there is a halo effect from treatment. Good examples here are asymptomatic malaria and asymptomatic COVID-19. Asymptomatic malaria carriers have been shown to pose a large public health risk (28), which, paired with the large magnitude of burden malaria brings globally, might have prompted more flexibility in the use of the medicine and approval by the EMA. The Ronapreve® case is a counterexample; it also can help to prevent asymptomatic spread, but perhaps due to the high cost and potential for side effects in patients, it was not recommended by the NICE. One can hypothesize that medicines in this quadrant will face greater scrutiny on side effects and cost, though this would require further research to confirm.

- Quadrant IV | the condition does not lead to mortality/morbidity, and there is no halo effect from treatment. An example here might be male pattern baldness; even if it is possible to detect it genetically years or decades before the onset of symptoms, treatments for asymptomatic cases are unlikely to be funded by public payers unless a link with mortality/morbidity can be shown.

### *4.3. Observation 3: There Is No Precedent for Assessing Drugs Treating Asymptomatic Patients in a Poorly or Loosely Defined Disease*

This research found that the treatment of asymptomatic conditions has only been explored with a narrow lens to date, where diagnosis is straightforward and indisputable. Each of these 8 drugs had something in common:

The diagnosis- and therefore patient eligibility- could be independently and objectively confirmed in a laboratory, either biologically or genetically. In contrast, novel treatments for AD, which by today's definition requires symptoms of cognitive decline to confirm, will bring a new hurdle not yet addressed by precedents.

### *4.4. Observation 4: There is Little Precedent for Assessing Drugs with Unclear Survival Benefits*

Prior to this research, it could have been hypothesized that one of the success factors in bringing a treatment to market for asymptomatic patients was the use of an established and validated surrogate endpoint. However, this research provides no evidence that an endpoint other than survival would be seriously considered, creating disappointing news for manufacturers hoping to seek approval and reimbursement with more creative evidence.

The only treatments for asymptomatic patients that received recommendations for reimbursement from NICE were Zytiga® for prostate cancer and SMA therapies. Zytiga® showed a statistically significant overall survival benefit in treating asymptomatic patients, which was possible given the short life expectancy of the condition. Spinraza®, as the trailblazing SMA therapy, also showed a survival benefit. Though the data were immature at the time of the NICE review, the committee deemed that beginning treatment during the pre-symptomatic phase would only increase the value and lower the cost per quality-adjusted life year (QALY). Zolgensma® and Evrysdi® were given similar leeway, meaning that agencies may not currently be equipped with frameworks to appropriately handle future treatment situations, such as in AD or Huntington›s disease, where treatment might begin in asymptomatic patients 20+ years prior to expected death.

### *4.5. Observation 5: Following the Footsteps of These Precedents May Result in Significant Costs and Delays in Bringing Much-Needed New Therapies to Market*

There are currently no disease-modifying therapies available for Huntington's disease and very limited options for AD. In both of these conditions, the disease builds progressively and may be biologically detectable up to decades before the onset of symptoms, suggesting treating in the asymptomatic stage- sometimes for many years- might bring the most benefit. However, studying overall survival in these settings would be prohibitively slow. Given that the only success stories in the EMA and NICE so far have been able to show overall survival, more research is necessary to establish how new medicines for asymptomatic patients can be successfully brought to the market.

### *4.6. Limitations*

It should be noted several limitations of this study. First, the search terms used to define the scope of the clinical trials search may be specific to certain diseases, and further work is needed to assess what precedents lie in other areas (for example, searching for "Stage 0"). Second, the analysis was based only on publicly available information, and there may be additional frameworks to address these challenges that have not yet been reflected in the literature. Third, the data were only analyzed from the NICE in the UK and the EMA in Europe, so the results may not be generalizable to a wider global context.

## 5. Conclusions

The introduction of novel therapies aimed to treat asymptomatic or pre-symptomatic patients years- or even decades- before clinical manifestation poses budgetary, medical, and ethical questions for which there is little to no precedent. A clear link between morbidity or mortality, preferably demonstrated through overall survival, will likely need to be shown in the short run, which might add to the costs and time required to bring much-needed new treatments to the market. As science advances, where the most benefit can be brought by treating conditions years before symptoms manifest, a new framework is needed to ensure that such innovations are encouraged, recognized, and ultimately made available in a sustainable way.

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