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The Role of Agentic AI in Next-Generation Drug Discovery and Automated Pharmacovigilance for Rare and Neurological Diseases

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Abstract

The world's first agentic artificial intelligence designer, established in 2016, was applied to and validated in drug discovery processes. The founders of the pioneer companies in 1994 and 2016 created nearly identical engineering principles, properties, and methods with diverse mathematical and logical variants. In design, discovery, and validation engineering, discovery engineering designs, discovers, and validates AI-managed flexible and highly selective ligands, with advantages in shaping and drug repositioning applications. The agentic AI role avoids random results of conventional AI by not creating pharmaceutically irrelevant knowledge from irregularities or artifacts in drug action data constraints. Its retrospective, when required, and forward pharmacovigilance identify unknown ligand problems and related molecular mechanisms for safe medications. Next, the candidate ligands that are already in their concepts and mechanisms of action can be free of real-world evidence at the time of being formulated as investigational new drugs or old drug license suspensions, which can remove the success delay in the ligand-to-market process and greatly diminish the winding drug discovery path of the tangible cost of drug development. The key biomedical AI potential and practical contribution to future global countries are the top-value discoveries of highly selective ligands with mechanism of action attributes returned as actual site determinants. High-value products are sold out without the need for sales costs. Their buyers are satisfied patients, clinicians, payers, and regulators. The fundamental variables that determine the compound action efficiency of all effective medicines that induce the end of disease can be modeled and individually quantified. Their common topological pathway can be predicted and validated with the experimental approach as discovery aims to create specific reactions of a single or small number of predefined chemical compounds with a single or small subset of predefined targets.

Keywords: Agentic AI, Artificial Intelligence, Drug Discovery, Discovery Engineering, Ligand Design, Pharmacovigilance, AI-managed ligands, Drug Repositioning, Predictive Modeling, Mechanism of Action, Pharmaceutical Innovation, Computational Drug Design, Targeted Therapies, High-Selectivity Ligands, Biomedical AI, Retrospective Analysis, Forward Pharmacovigilance, Investigational Drugs, AI-Driven Drug Development, Topological Pathways.

1. Introduction to Agentic AI in Drug Discovery

Agentic AI refers to AI systems that are capable of operating autonomously and making decisions. They are typically built from multiple AI technologies, such as deep learning, symbolic reasoning, reinforcement learning, and soft computing, to create integrated, multi-strategy systems. In this discussion, "agentic" indicates the capacity to be an agent—that is, to act, make choices, and make decisions. These systems are often embedded in robotics or control systems. In the life sciences, agentic AI has thus far focused on healthcare settings, treatments, or diagnostics—most of which are reactive when the patient is already sick or has a condition. Only a few agentic AI systems are currently used, and these are largely for diagnostics. We argue that in drug discovery, agentic AI will be a pioneering method and that it could potentially revolutionize the development of new drugs to treat many conditions, including rare and neurological diseases.
Machine learning allows us to mine vast amounts of diverse data and draw out hidden insights. In an ideal setting, and based on well-implemented computational and experimental methodologies, AI pharmacovigilance could signal potential unwanted events long before the first-line therapies are used on humans. Pharmaceutical R&D has done well to integrate genetic findings linked to targets with the drugs already developed, rather than going down the route of studying the normal function of the target from scratch and then developing a drug. The solution is to develop compounds not to normalize a target but rather to destructively affect it. Agentic AI would provide transformative tools for the above areas. The very essence of agentic AI—the ability of these systems to operate autonomously and make decisions—would make this technology transformative to drug discovery.

1.1. Definition and Characteristics of Agentic AI

With the advent of the digital revolution, the interplay between the power of computing and data has become the main focus of the AI field. In this paper, we limit the scope of AI to digital systems that are autonomous and able to reason and make decisions without direct human intervention. We refer to these as Agentic AI, and the form of AI most typically encountered in drug discovery is referred to as Agentic AI-in-a-Box. These are non-human healthcare professionals who do not require

appropriate qualifications or licenses to make decisions or to provide medical care. The characteristics of Agentic AI are: • Autonomy. Agentic AI can operate without direct human intervention. • Adaptability. Agentic AI can change its behavior in response to different challenges or environments. • The ability to learn. Agentic AI can learn from examples or experiences, or the results of its previous decisions. • Making decisions based on data. Agentic AI typically makes decisions by analyzing and comparing information given to it in the data and acting on the best available information it has. Depending on their specific characteristics, Agentic AI systems might also be able to self-improve or comprehend the context of the data they work with at a deeper level. These characteristics make AIA-Bs especially suited to working in the complex field of drug discovery, where there are many uncertainties, data are often missing, and understanding is incomplete. Agentic AI systems are prepared to deal with uncertainty and can adapt to work with missing or poor-quality information. Good AIA-Bs could adapt to deal with unforeseen circumstances and apply their decision-making process to a different project if their existing one is no longer feasible.

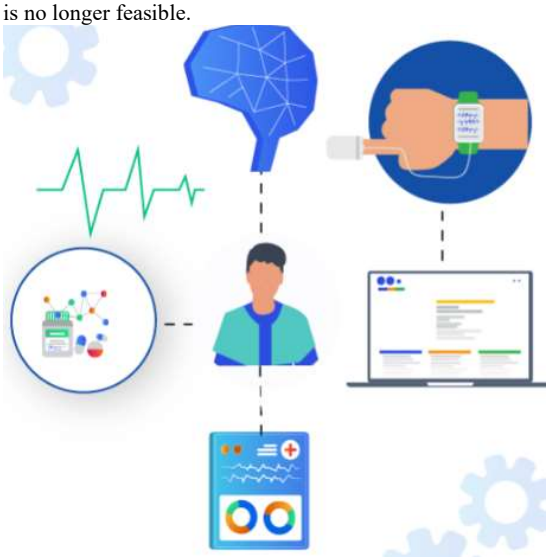

Fig 1 : Definition and Characteristics of Agentic AI

1.2. Historical Context and Development

The domain of present-day agentic AI has a rich historical context that reveals its gradual nature, as there is a long lineage of systems that perform various tasks autonomously within the pharmaceutical industry. In 1988, a system was developed that autonomously planned the synthesis of water-dispersible carboxamide polymers and verified their drug-like behavior. Continued development of the capability to autonomously develop potential drug candidates occurred. A system was developed to predict toxicity in systems that could take electron density maps from crystallography and derive from them a structure with functional data. At its foundation, this system consisted of a set of logic program rules applied in a rule-based way. Scripts were developed that could process data coming from high-throughput screening to iteratively produce models that predicted a probability of discreet bioactivity for a molecule.

Statistical learning algorithms were utilized for function discovery over databases. A classic in AI was created: Genetic orithm Directed Combinatorial Targeting Using Liquid-Phase Chemistry. Starting in the early 2000s, these techniques were co-opted and applied at the cutting edge of the field at the intersection of bioinformatics and AI at firms now in history. In the pharmaceutical technology literature, such technologies operate under the aegis of computational biology and later from data science. Despite popular belief, with a few notable exceptions, these technologies are not held back by computational or biological constraints but by known chemical issues. The chemical issues are not related to synthesis but instead to drug selection. AI technologies for medicine are primarily concerned with the selection of drugs; this endeavor is fraught with embarrassment. As such, when viewed in the historical context, these technologies have a historical backdrop of capabilities that were driven by the imperative of making the necessary "closed-world" assumptions that artificial systems typically require, even at the level of molecular representation.

The last decade and a half have, however, witnessed the development of truly agentic AI, or a class of embedding technologies that develop and execute capabilities based on observation and ingestion of open-ended external conditions. The creation of a notable drug discovery engine suggests that the field is ripe for understanding. Unlike all the other historically advanced AI-embedded systems, this system had few independent assumptions about the problem it was solving. It could dissociate the information from the data. These traits suggest an agentic system vocabulary.

2. Challenges in Drug Discovery for Rare and Neurological Diseases

Discovering novel therapeutics, especially for rare and neurological diseases, is a multi-faceted challenge due to the complex nature of the diseases. Rare diseases, with over 7,000 known diverse indications, often have heterogeneous clinical profiles and intrinsically varied biological pathways. The little data that do exist are usually noisy due to small sample sizes and confounding factors. Furthermore, the collection of additional patient data is inherently more challenging as suitable patients are scarce and fragmented through tens to hundreds of healthcare providers, sometimes in different countries. It is thus typically very hard to build an accurate outline of the characteristic expression profile of a given rare disease through public data

repositories. The pervasive biological heterogeneity typically stands in stark contrast to the common genetic drivers behind the disease, which can be deduced. For neurodegenerative diseases, an estimated 50 million suffer from these diseases, but only 2% of clinical trials are in this space, and at least 20 drugs have been approved for symptoms, topical therapy, and supportive care.

Pharmacovigilance for these diseases, especially in the pediatric population, is severely lacking, and the adverse event signal detection and policy for these diseases may require more initial investment as the regulatory environment adjusts to the right-to-try legislation. The limited data for and variability of rare diseases make it difficult to successfully model these diseases and hence find suitable drug targets. On average, the required effort to bring a new treatment to market takes about 16 years. Therefore, rapid prototyping for rare or neurological diseases can have an impact in places that are purely computational and can be more rapidly developed and implemented, independently from often approving first-in-human trials. Combination therapies to attack different parts of the pathways are also receiving increasing focus given the spectral involvement in various target diseases.

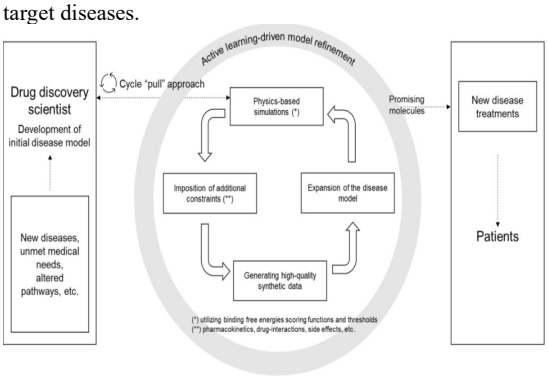

Fig 2 : biopharmaceutical drug discovery

2.1. Complexity of Disease Mechanisms

One of the hurdles when targeting rare and neurologic diseases represents its 'mechanistic' complexity due to the interplay of often unknown genetic, environmental, and biological factors. As a consequence, dissecting these mechanisms is an enormous challenge, where the lack of a clear understanding of many of the diseases limits patient stratification and thereby encumbers the identification of valid therapeutic approaches. For many neurodegenerative diseases such as amyotrophic lateral sclerosis and progressive supranuclear palsy, for instance, these 'mechanisms' remain elusive; they are largely undescribed, or at best, may be only modestly causally associated with disease pathophysiology, or they may be associated primarily with late-stage disease progression. An illustrative example of a muscle disease is the molecular switch from DMD to BMD caused by increasing prevalence later in the protein. In neuroimmune diseases, it is even more remarkable that despite progress, the only drug approved for ALS remains targeting glutamate signaling, which elicits a modest and not always relevant effect. Examples of rare neurological and other orphan diseases suffering from the same mechanistic lack of hypotheses are indeed too numerous to mention in this short review.

To date, rather than a complete understanding of disease mechanisms from mid- to late-pathology, as often remains the case for rare and orphan diseases, early-stage promiscuous hits are identified first, most often via human genetics, which thereafter are associated with pathways. mRNA expression, RNAseq, genome-wide association, epigenomics; molecular (phospho)proteomics; also interactomics datasets, and methylation arrays reflecting alterations in the signaling or molecular pathways in disease have been published, profiled, and analyzed via different computing platforms. Addressing several systems and pathways in parallel not only requires an ever-dynamic toolset and analytical approach, which is quickly antiquated, but also brings to mind the realization that, inter alia, filtering based on prior knowledge, tools, or techniques such as cell-target or tissue specificity rather hinders the potential for novel target discovery. Where communities studying neuroinflammation fail, others such as the cell and gene therapy community as well as the rare disease community aim to pick up the greater push toward basic science explorations into obtaining a more comprehensive understanding of genetic complexity in neurodegeneration and other rare diseases.

Equation 1 : AI-Driven Drug-Target Interaction Prediction

$$S_{ij} = \sigma\left(\sum_{k=1}^{n} w_k f_k(D_i, T_j) + b\right)$$

S_{ij} = Interaction score
$f_k(D_i, T_j)$ = Feature function
w_k = Feature weight
b = Bias term
σ = Activation function

2.2. Limited Patient Data Availability

Collecting patient information is a vital aspect of uncovering the multifaceted roots and outcomes of rare and frequent neurological disorders. However, due to a lack of awareness, the limitation of access to healthcare, along sparse funding, there are instances where an individual may seek a genetic assessment for a neurological malady to no avail. Moreover, such an

extensive paucity of clinical trial investigators for a given disease indicates that the trials may not be conducted quickly or in a patient cohort that neatly matches the disease. This problem grows even further from an inadequately sized cohort for statistical significance. Sometimes, these studies are launched on an insufficient number of patients to represent the whole scope of suffering patients, which we hopefully conclude is the motivation and logic behind acquiring more patient records. Smaller patient populations compound a lack of statistical representativeness and can impede our collective ability to comprehend what medications are about to do in systemic and patient-specific harms. A multitude of possibilities can hasten the analysis of patient data. Matters of ethics, privacy, and regulatory compliance amplify the importance of attending to these types of limitations. Additionally, safeguards to minimize misclassification in electronic health records register image quality limitations, including scanner noise artifacts, that could have an especially large impact on the reproducibility and interpretability of real-world evidence brain morphometry research. Considering the downfall of comparing group outcomes from rare or neurological disease trial settings, there exists no established and ethical substitute except to initiate measures leading backward – to transform these dashes into marathons: this is the essence of patient-led research gone pandemic: put the patient at the patient and investigator level. Innovative solutions include informatics that monitors interactions among genes and the environment. These are applied to extensive patient-enrolled registries harnessing in-house research, diagnostic, and biobank resources, all fueled by the centralized efforts of the International Rare Diseases Research Consortium. Further, analyzable enlistments are predominantly trains of entire pedigrees and encompass largely hereditary disease reconstruction inputs, plus tomorrow's today: particularly fertile ground for emerging digital platforms heavily involving the patient and a pressing response for those very few willing to lend a hand. Genomic interrogation supports novel low-cost gene identification strategies, including the rapid validation of pathogenicity: the Genome Precision Medicine bed-to-bench-to-bed refactoring approach synchronously assists these research efforts. In an environment where we explore rare and neurological diseases, including orphan medications, for the detection of new off-label indications and genetics-guided agents, these living Digital Twins in healthy disease opposition trace any underway are fitted with Next Generation clinical trials defined below.

3. Current Approaches in Drug Discovery and Pharmacovigilance

Conventional approaches in drug discovery are expensive, systematically fail to deliver compounds to patients, and are often not properly aligned with the therapeutic needs of patients. Drug discovery involves several phases starting from target or gene identification to determine the role of a gene in a pathology, including systematic screens to identify compounds that modulate target or gene activity and subsequently in vitro cells or in vivo preclinical models to determine drug effectiveness. These phases are costly and are not always fully aligned with either new knowledge or patient insight. Late failure in clinical trials is a major issue for the drug industry, particularly for therapies in rare and orphan diseases or, in general, in diseases of the central nervous system. Clinical trial success has been flat for many years, meaning only a small percentage of phase 1 programs will result in an approved drug.

Moreover, it is estimated that, on average, a significant percentage of drugs that reach Phase 3 trials fail, most of them between Phase 2 and Phase 3. Lack of efficacy or safety are the primary reasons for failure. The reasons for such high rates of attrition are multifold, but an important contributor is the fact that re-engineering is difficult and risky due to the sheer volume of patients required to demonstrate a difference from the standard of care. Hence, to mitigate re-engineering risks, drugs must receive a proportionally lower rejection likelihood in phase 2 and preclinical phases of drug discovery. Conversely, if fewer patients are needed for a successful key clinical study, it increases the chances of being able to recruit them (for those that are small populations) and reduces cost, time, financial risk, and uncertainty. Given the need to be stringent in selecting a program for phase 2, overall this arbitrates for higher risk or best-evidence-driven selection.

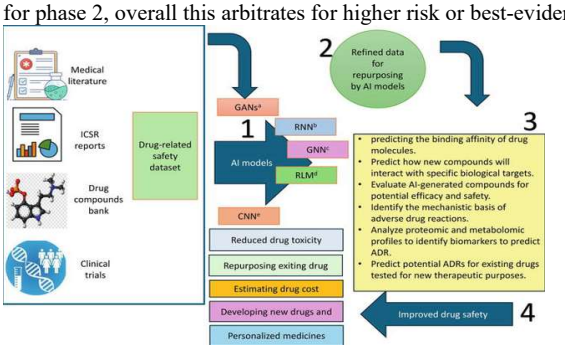

Fig 3 : Application of Artificial Intelligence in Pharmacovigilance Practices

3.1. Traditional Methods and Limitations

Historically, drug discovery is a multistep process that often begins with target identification, validation, and an early hit or lead. The lead might be used in phenotypic, target-based, or ligand-based assay formats to identify compounds that reverse the phenotype of disease or advanced compounds based on molecular mechanisms of interest. New leads are then further validated in a series of biochemical or cell-based assays to determine specificities, toxicity, structure-activity relationships, and pharmacokinetic properties in parallel with iterative in silico drug-property predictions. Over time, the compounds ideally become drug candidates, undergo safety pharmacology and toxicology testing, and then are introduced into animal models of human disease, eventually reaching Phase I, Phase II, and Phase III clinical trials. The process is characterized by a high level of compound attrition, long development timelines, and high costs, where a percentage of new drug investment in discovery will fail in regulatory review.

The conduct of all traditional drug discovery processes is driven by empirical data, but human-acquired experiences may not

capture the nuances of rare diseases that might be critical for disease onset. For most rare and neurological diseases, patients can routinely expect longer drug development timelines with high attrition rates, on the assumption that late-stage clinical trials will negatively impact patient outcomes. The scope of the problem is large, as there are roughly 7,000 different rare diseases that affect a significant portion of the global population, many of them drug-naive, with an average approval rate for drugs and biological products of about 40% in clinical trials over the past five years. Given the current limited gaps in therapeutic options and insufficient understanding of rare diseases, there is a significant concern about the rising costs of orphan drugs. Overall, the traditional way of doing drug discovery will impede our ability to cope with current and future healthcare needs. Applying agentic AI to this area could substantially streamline drug discovery and make it less biased and more informed.

4. Applications of Agentic AI in Drug Discovery

The application of agentic AI in drug discovery processes is manifold. Agentic AI can be taught to screen through millions of possible compounds or test experimental designs in a fraction of the time it would take otherwise. While traditional methods of creating and testing chemical compounds require time, labor, and a very careful understanding of molecular interactions, AI can predict the efficacy of a compound based on its potential interactions. Simulating the interactions of a small molecule with another protein, or assessing potential drug effects on a cellular model can all be predicted with a degree of accuracy using state-of-the-art AI. One can also predict potential drug-disease relationships by searching through vast amounts of biological, chemical, and clinical data, suggesting which compound model would be a good addition to a clinical trial. AI can be leveraged in drug repurposing efforts, indicating novel uses for already approved or discontinued drugs.
While no AI can design new interactions from scratch, the ability to generate new information from existing knowledge is revolutionary. Tailored AI models can be trained for target identification or compound prediction, depending on the desired focus of a clinical research question, whereas surge pricing models or in silico modeling can be used from start to finish of the drug development process, providing decision support for ascending validation steps. Decision-making AI drives the first phase of a drug development process by identifying promising drug targets. Prediction AI simulates pathway analyses throughout the various phases of a research project as a follow-up to hypotheses already being tested in the lab. The continuous interaction of these two, adapting to new data, drives methods of decision-making – making modifications in the lab to ensure the successful strategic scope.

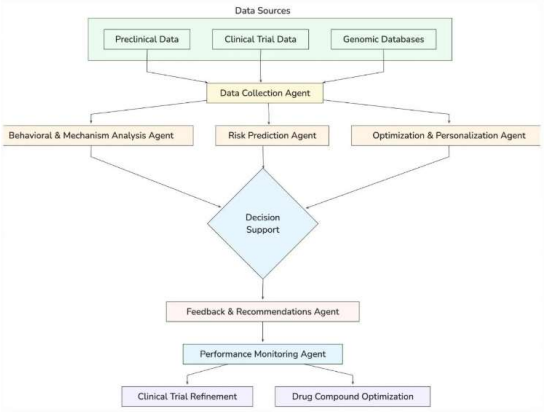

Fig 4 : Agentic AI to Accelerate Drug Discovery

4.1. In Silico Drug Screening and Design

The application of AI to in silico prediction of drug activity, commonly known as in silico drug design or silico drug screening, has been shown to predict drug-target interactions with high accuracy when reinforced with big data. In silico refers to computational methods that recap drug interactions or predict the downstream activity of drug-regulated proteins by merging informatics and biological data to identify therapeutic effects or adverse events. Such algorithms use knowledge from various biological databases collectively, which would otherwise require many hours or even days to identify and evaluate. Silico screening using various algorithms is commonly engaged in drug discovery to search for binding ligands that interact orthosterically or allosterically with a protein or other target of interest to predict potential new active compounds. These can be developed into new drug candidates, offering a time-effective exploration step to validate experimental work and therefore avoid or minimize the losses caused by ineffective research experiments. In addition, the off-target potential of a lead compound could also be evaluated in silico to avoid toxicities in preclinical or clinical studies, offering several patient safety benefits in a rare disease population.
Machine-learning predictive algorithms also offer the potential to design new compounds from scratch, in a process known as de novo design. De novo drug candidate generation programs have historically been useful in accelerating the drug discovery process for hundreds of patients, most prominently via the computational design of small molecule inhibitors against protein kinases, an approach that has led to the development of marketed drugs for leukemia, cardiovascular disease, and many other disease areas. This concept not only drastically changes the traditional hit-to-lead discovery paradigm but, if successful, also revolutionizes the number of therapies available to undiagnosed or rare disease patients since de novo generation of compounds by AI and in silico screening algorithms is less frequent in rare or undiagnosed disease areas to date. Techniques used in such de novo design algorithms focus on virtual chemistry that predicts or is programmed to rapidly sample vast numbers of organic compounds from skeleton scaffolds such as pyrazole, pyrimidine, or a-diketone, before altering these via virtual reactions.

This rapidly generates on average hundreds of millions of unique compounds for evaluation and thus reduces timeframes for lead generation. Some AI-based in silico evaluations can also verify or optimize lead compounds that are developed in the laboratory; this process is known as lead-hopping or lead optimization.

$$R_t = \frac{O_t}{E_t} = \frac{\sum_{i=1}^{m} I(A_i, D_i)}{\sum_{i=1}^{m} P(A_i, D_i)}$$

Equation 2 : AI-Based Risk Signal Detection

R_t = Risk ratio

O_t = Observed events

E_t = Expected events

$I(A_i, D_i)$ = Indicator function

$P(A_i, D_i)$ = Predicted probability

4.2. Target Identification and Validation

Disease mechanisms, or so-called mechanistic processes, refer to biological and biochemical perturbations coupled to a particular treatment indication, that is, the disease. The process of selecting molecular or cellular processes that can serve as entry points for a molecular personalized intervention has been termed the basis for generating promising consumer safety outcomes, backed with comprehensive pathophysiological and physiological data, in turn, grouped under the ideally isolated "compelling demonstration of the mechanism of action." Target identification is the systematic process by which one selects targets—molecules in the context of drug discovery—that can become objectives for the rational design of therapeutic intervention. This is a very complex undertaking, as many diseases cannot be considered monocausal phenomena involving one gene or one biological process.

Some of them are rather polygenic or multifactorial (i.e., many genes contribute significantly to producing a phenotype that can be associated with a pathological condition), and only a certain fraction of them can be reduced to this fundamental combinatorial of biological events. Target validation (or the demonstration that a process is of interest to be intervened with as it is coupled to the pathological state) can be initiated once some information is available regarding some experimental or clinical observation that is suspected to be mechanistic. Although target identification and validation at present do not employ directly agentic AI, a convivial AI is stretching from either proponent learning or bootstrapped processes that are based on the same fundamental concepts, making the development of a combined agentic AI approach feasible and reasonable. The program aims to find the preictal target of genes ripe for agentic intervention. The initial priority in target identification is to pick "viable" proteins that are significantly forced because they balance the situation in which they are used.

These proteins—targets—are hence supposed to be "druggable," a term sometimes also intimately linked to the terms "developable" or "tractable." Targets will typically fit into one of five classes: enzymes; receptors; ion channel carriers; and other mechanisms of action when there is no clear classification. In the period of these symptoms worn by modalities; receptors, peptides, and better proteins or antigens may commonly be solved; and alleles, gene therapy, and pathology discovery are the topmost possibilities in the long-term value period. The latest approach may provide additional insights and preparations of drug candidates for agentic engagement based on this technology, but the technology is beyond the current effort. For those targets that intercommunicate, the developers shall be obliged to seek backing from the team for the development of agentic-ready targets as delineated above.

5. Agentic AI in Automated Pharmacovigilance

Agentic Artificial Intelligence in Automated Pharmacovigilance

Automated pharmacovigilance, the real-time monitoring of adverse events associated with pharmaceuticals using AI, has undergone explosive growth recently in capabilities and use. Without question, one of the strongest features of AI is its ability to process data – case reports, EMR and EHR data, medical literature, etc. – and put it to use in new ways. This is no less true in the context of identifying and managing risks associated with medical use. By making increasingly rich and complementary datasets of safety and usage both highly colocated and thus highly available and beneficial, we as a community have developed a capacity for real-time automated and incremental discovery and continual learning of the risks associated with the medical use of pharmaceuticals. With the ability to collect, manage, and analyze very large sets of data from patient reports, health care records, social media, and other diverse sources, Agentic AI triages and prioritizes adverse medical event reports collected from diverse sources, recognizing and classifying these reports of potential safety signals based on patient reports, information taken from clinical studies, combined evidence from case reports and well-designed clinical studies, and case reports with information from digital biomarkers. In addition to assigning reports to medical review, automated pharmacovigilance uses AI systems to rapidly assess the quality and completeness of case reports based on structured safety records.

Having categorized the information, Agentic AI facilitates accelerated triaging of safety signals for immediate review, setting rigorous description/response criteria for signal management. The capability to aggregate and initialize real-world evidence quickly enables the ability to call safety or risk events that would not have been previously captured using traditional forms. As mentioned previously, AI can work with multiple datasets, identify conditions, and derive additional data to verify if the association exists. AI makes recommendations about how to mitigate potential risks identified in the evaluation process, such as adding warnings and precautions. In addition, AI also reviews to verify whether, anecdotally, similar dysphonia reports exist. AI has established clear response times related to these patient symptoms that are consistent with guidelines for expedited

reporting, where required. Further, recommendations match criteria for when medically the same cases can be counted as one report. In the following, we provide a more detailed view of these various process steps and detail how AI systems can work with complex global regulatory standards and patient diversity to protect patient safety and support reasonably rapid access to new medical interventions with acceptable safety and efficacy profiles.

5.1. Real-time Monitoring of Adverse Events

Today, companies are developing systems with agentic AI elements that can continuously monitor adverse events as they happen, aggregating data from multiple sources to ascertain their significance. An increasing amount of information is generated by AI systems or can be made available for AI. These real-world data can give a good picture of the occurrence and the temporal relationship of adverse drug reactions and other safety information. This is especially important for adverse drug reactions that occur rarely and might thus not have shown up in clinical trials. Conventional signal detection processes may be less effective in understanding rare adverse drug reactions. Given the vital need for this safety information, these systems need to deliver this intelligence as promptly as possible.

It is well recognized that better understanding adverse events would greatly enhance our efforts to prevent them. Delays in recognition and characterization of adverse events can compromise safety as they leave loosely defined boundaries of our safety architecture. Continuous monitoring is crucial to the growing field of rare and neurological diseases as well. Several data sources might be employed in real-time monitoring, from hard sources like electronic health records, serious adverse events, special studies, and patient-reported outcomes about adverse events to soft sources like spontaneous reports. The latter is influenced by, among other things, regulations, and their tight structure. They are nevertheless potent sources of safety information, especially useful for the fast alerting component of this system. Working together, the power of aggregated data sources can come to fruition in providing predictive insights and driver-based pharmacoepidemiology. With the aid of natural language processing or another form of machine learning, unstructured information can, far quicker, be assessed for signals as well as informing and prompting queries. Running in the background, the system can also aid and enhance the safety surveillance activities of healthcare professionals, entities, and regulatory agencies. Ensuring that real-time data is accurate comes with its own unique set of problems given the difficulties of checking multiple information sources and ensuring the reliability of data surrounded by intense interest, as well as psychotic patients and intelligent, organized interest groups. AI has a significant role to play eventually in communicating between healthcare professionals facilitating accurate, quality adverse event reports, and removing any transmission bias behind recorded adverse events. The real breakthrough might be the entrance into communities and uncovering dangers latent in pseudo-anonymous areas of social networks, but verification and validation are particularly active fields in the construction of these systems. For some, drawing information from online sources may be regarded as a mixed blessing given its potentially biased nature, but yet it can capture early unmet needs information from patient voices when traditional sources do not suffice.

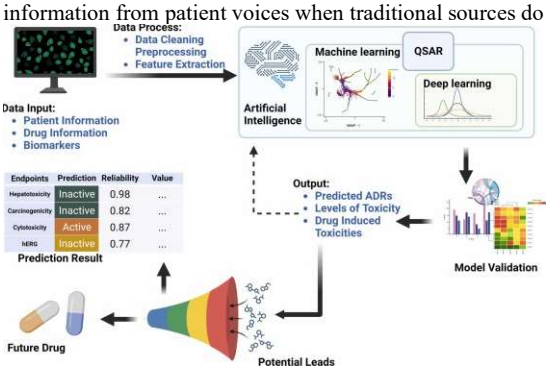

Fig 5 : machine learning in early detection of adverse drug reaction

5.2. Signal Detection and Risk Assessment

In automated pharmacovigilance, agentic AI can detect and interpret safety risk signaling, transition, and substitution in the rapidly evolving therapeutic landscape. In this setting, signal detection strategies should be adaptable according to the available data or the characteristics of novel drug therapies from adverse event reports. Pattern mining tests whether the combination of co-occurring drug and side effect terms is significant. Knowledge integration techniques extract knowledge from various reporting sources or supplement data. AI methods are particularly well-suited for signal detection processing, especially as they can analyze multiple diverse data sets simultaneously and have strong data abstraction and pattern recognition capabilities to define a broad variety of possible signals of drug-induced injuries. For potential clinical significance, the mining of EHRs, which reflect common clinical practice, should also be implemented into post-marketing surveillance. A contrarian end of the spectrum, reflecting that an increasing number of physicians self-finance their medicines, is individual case tracking and reporting.

The latest generation of commercially available artificial intelligence algorithms, referred to as agentic AI, can analyze multiple diverse datasets, often in an adversarial manner, thus producing a nuanced understanding of the relative risk factors associated with the varied robustness of different drug therapies. This intricacy can also reveal safety signals that were earlier missed due to being downranked in the current human-processed system of linear hypothesis generation and testing. Agentic AI's signal detection methodologies can have an instantiation of different signal detection methodologies being applied in informatics. For instance, signal detection using agentic AI can employ advanced data visualization analytics including micro interaction detection, interest crowd graphing, and event prediction modeling. The entries from data are used to inform the AI on both known side-effect profiles and prevalence of side effects and for binary output with supervised learning on labeled evidence, either through retrospective case-control studies or forward-targeted prospective surveillance studies. Lastly, it's important to

note the requirements of potential integration approaches. Short-term signal analytics do not replace extended assessment for risk-benefit calculation in anticipated evidence generation regarding drug-induced adverse effects. As such, domain specialists and qualitative triangulation approaches are integrated to deliver early warning functionalities that complement but do not replace, current methods of signal detection for pharmacovigilance. Identifying adverse drug events is a fundamental component of modern drug safety. Opportunities and challenges in automated pharmacovigilance are discussed. Importantly, as pharmacovigilance moves towards analyzing first experiences with drug therapy, a retrospective evaluation of drugs and biologics producing injuries from randomized controlled trials, surveillance cohorts, or community adverse event reporting data may be necessary. Restricting rejuvenation therapies under potential conditions in narrowed experimental frameworks could improve risk-benefit ratios in clinical deployment.

6. Ethical and Regulatory Considerations in Agentic AI

The pursuit of biological relevance in agentic AI for drug discovery and pharmacovigilance is ethically sensitive and has implications for regulatory implementation. Decentralization will separate data from the institutions collecting it, but care will need to be taken to respect the privacy of people contributing data to the open AI knowledge commons. Rare and neurological diseases are methods of ethical trustworthiness, wherein drug repurposing is an ethical practice and whose populations may contribute time, data, and a stakeholder role for knowledge development. Integration of patient immune cell functionality may be costly or painful, yet researchers are increasingly innovating to account for variability in various routes, such as decreasing blood volumes in trial registries bearing ad hoc design and descriptive results.

The same access risks arise in collecting patient descriptions and novel mechanistic knowledge, and the same principles for planning AI healthcare research respectfully apply to aggregating and separating all of these data. In the multi-payer marketplace of Europe, there may be a significant understanding and consensus about the efflux capability of pharmaceutical manufacturers. AI-driven decisions may also have legal and ethical implications, particularly in the context of medical decision-making involving individuals who may have the right to receive explanations of an algorithmic decision. Supplementing the impending ethical guidelines for AI, the European Commission assented to the AIF Act and the European Health Data Space Regulatory Proposal. These proposals aim to address the ethical and legal challenges brought about by the interaction of AI and patient data for clinical predictive modeling. Data reuse beyond the patient is legal in this manner if the AI was developed using appropriate anonymization and patient privacy and professional expectations were taken into account by the developers. It is the collaborative duty of developers, clinicians, and the regulatory body to uphold the spirit of these ethical and legal standards through the research and development process to maintain trust and apply agentive AI in pharmaceutical research.

6.1. Data Privacy and Security

While the addition of personified communication agents to automated pharmacovigilance may have several potential benefits, it poses several privacy and related ethical challenges. One of the key issues here lies in securing the sensitive health data of patients against the risk of unauthorized access and data breaches. Ensuring the compliance of AI applications with several regulatory frameworks aiming to ensure sensitive data handling might be extremely challenging, if not outright impossible. Ensuring secure patient data handling in Agentic AI pharmacovigilance requires verification that several security measures, including encryption, anonymization, and pseudonymization, are in place to ensure patient confidentiality. Agentic AI applications further have to ensure the security of stored confidential patient data through secure, access-restricted database administration systems. Agentic AI pharmacovigilance requires the secure and compliant handling of sensitive health data. Such privacy assurance mechanisms include secure data encryption, pseudonymization, anonymization, and secure storage solutions. Confidentiality and trust between healthcare providers and patients have to be maintained, and security measures have to be in place to protect sensitive patient data from both insider and outsider threats. Security mechanisms should be checked and potentially updated regularly to mitigate evolving security risks. The quality of Agentic AI content further has implications for the robustness of pharmacovigilance reports generated and might affect the trust in the use of the content. Security updates thus have to be implemented by developers.

6.2. Bias and Fairness in AI Algorithms

From the perspective of drug discovery and pharmacovigilance, algorithms trained on biased data can potentially make flawed decisions about which medicines to investigate further, favoring candidates that appear to work better in certain populations while overlooking effective medical agents with broader applications. A lack of diversity in the collection of dimension values in training data is often the root cause of bias. Any marginalized group can become the inadvertent casualty of biased AI-based decision-making. While demographic attributes (age, gender, sexual orientation, race) have received the most attention concerning bias and fairness in applications of AI in effecting healthcare delivery, other dimensions yielding guidelines for the lawful processing of health data emphasize that health information should be utilized to individualize healthcare delivery. Performance metrics should, as a result, account for the needs of clinical sub-groups of patients and healthy individuals, while penalized axioms should offer a scale-up of care delivery to enhance public health, including difficult-to-reach individuals. It is well recognized that ethical and cultural concerns are also key in ensuring negative inferences about a set of dimensions are not silently buried through the subspace mean. Socio-economic biases in the decision-making process of some healthcare delivery algorithms should eventually be made transparent, especially to the individuals concerned.

Technical reports recommend best technical practices that data scientists and algorithm designers should adopt to ensure the responsible development of AI and AI systems that are incentivized to consider the course for better, less biased AI systems. First and foremost, AI and AI systems must be designed with the intent of treating individuals and community groups with accrued sensory and interpersonal skills with fairness. Fairness should be part and parcel of any transparent description of the end goal—the objective function of the AI algorithms that drive choice or AI systems that learn a preferential ordering that can be interpreted. Even with the description, or operationalization, of the design optimization, AI developers, hospital system

directors, or government ministries that procure AI-based hospital systems should themselves acquire the capacity to audit these systems to assess if they work with fairness and are consistent with existing societal healthcare goals. Optimal hospital system designs should, for example, not be based on the color of your skin.

7. Case Studies and Success Stories

Case study: Collating crowdsourcing data to enhance computational screening Case study: Next-generation patent for Amantadine Success story: Improving blood-lung oxygen bioavailability Success story: Expanding the use of existing pharmaceuticals for COVID-19 The case studies and success stories highlighted in this section share their application of different AI-driven methodologies in the context of drug discovery. AI and big data processing enable the identification of novel drug candidates in rare and difficult-to-treat diseases, and the ability to automate evaluations to produce a clear and comprehensive pharmacovigilance report with all related big data analyses on those drugs that have the potential to be approved. The Agentic AI subfield has been explored to ensure high regulatory confidence and shared learning and application of such methods collaboratively. This section indicates that we now possess functioning and pragmatic solutions to some of the challenges facing us today. The five case study vignettes collectively explore successes and/or the lessons learned from demonstrating the implementation of different AI methodologies. Takeaways spotlighted from these case studies demonstrate a clear indication of how and where AI can further be utilized in the pharmaceutical industry, both now and in the foreseeable future to address a variety of disease-related challenges. Furthermore, the four stories present specific areas where AI has improved drug discovery and development, benefiting disease patients. They celebrate the ongoing success stories of drug discovery projects that are already making significant medical advances toward the treatment and management of a variety of life-changing and life-limiting diseases. Each story showcases a different way and different areas where AI and drug discovery are working collaboratively and cross-phase, benefiting the disease patients for whom they are intended.

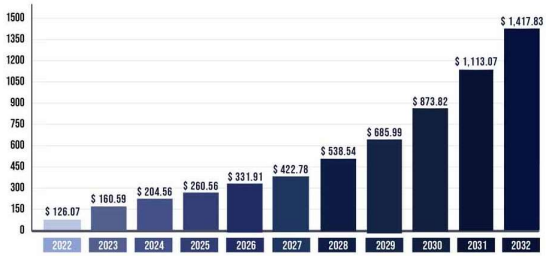

Fig 6 : Advantages of Gen AI in Drug Discovery and Development

7.1. Examples of AI-driven Drug Discoveries

The past five years have seen an explosion of drug targets and therapeutic candidates developed through AI technology. Examples include therapeutic candidates in metabolic diseases, and neurodegenerative diseases, such as Alzheimer's disease and Huntington's disease. Other targets proposed include idiopathic pulmonary fibrosis, as well as using de novo generated stereoisomers of approved drugs targeting neuromuscular disorders. A whole family of proposed therapeutics for Duchenne muscle dystrophy was generated in silico and experimentally tested. An unprecedented combination of compound multiplex multi-omics screens both in vitro, in silico, and in vivo has proposed a novel approach for deconvoluting both the molecular networks underlying rare diseases, such as diabetes insipidus, and very rare diseases such as "Michelin" baby syndrome. In several cases, active follow-up systems pharmacology models have provided additional support to the bioactive proposed network strategies.

The development of drugs has been laborious in the past, and drugs for diseases such as Alzheimer's or Huntington's diseases, as well as rare diseases such as tyrosinemia, are considered high-risk, high-reward. Here we show that numerous de novo discovered therapeutic candidates, initially generated from disease-specific polypharmacological networks, have been experimentally tested with success rates of 67-100% for ten such targets. To generate plausible discovery hypotheses, we made use of a range of algorithmic AI technologies, including drug repositioning AI, ligand-based ligand-target similarity networks, and shortest path analysis. Expert input on the polypharmacology of reviewed drugs and potential links between the drug targets of existing drugs was used for "ready-to-use" strategies. For new targets, similar heuristic strategies were updated and verified for local topology. This multi-staged, high-dimensional multi-omics, multi-scale workflow was validated by active users.

In many cases, the healthcare professional was closely involved in this process and in testing drugs on patient-derived material. For instance, Ldn159 on patient-derived microglia induces a plastic phenotype with observed increased progranulin transcripts likely consistent with reduced microgliosis. The content of Table 4 is mostly under publication review or in discussion with expert curators; hence, it is disclosed here, but information at this time is limited. An EU research grant has been recently granted based on the in silico and in vitro generated projects.

$$Q(s,a) = r + \gamma \max_{a'} Q(s',a')$$

Equation 3 : Reinforcement Learning for Drug Discovery

$Q(s, a)$ = Expected reward

r = Immediate reward

γ = Discount factor

s' = Next state

a' = Next action

8. Future Directions and Opportunities

1. Emerging Trends In recent years, AI has achieved an increasing impact on drug design and development processes, with notable tools and applications such as molecular docking, virtual screening, and protein structure prediction. Moreover, emerging trends reveal the development of new AI technologies that are specialized to further improve these processes. For instance, a consensus highlights the upcoming integration of multi-omics data to predict the likelihood of a patient's response to a drug. Additionally, advanced algorithms in machine learning and deep learning can connect molecular and protein chemistry with various omics and phenotypic data sources, and can also model and predict the likelihood of adverse effects of developed targets and/or compounds. These are especially important in the case of rare diseases and neurological disorders, where there is limited patient data and increased variability that must be taken into account. Another trend is the integration of multiple sources where machine learning can be used for natural language processing across databases to identify new connections between diseases, proteins, molecular mechanisms, and drug effects.
2. Opportunities and Barriers One of the main opportunities that have arisen recently is the opening up of novel mechanisms of action, without prior target hypotheses that would not have been possible using traditional approaches. This could mitigate the cost and speed up the drug discovery process, as well as help to identify new potential uses for existing drugs. Moreover, these models could address a significant unmet medical need for patient personalization. Based on our interviews, a multi-stakeholder collaboration between industry, regulators, and data privacy experts can address a critically underserved market—rare and neurological diseases. If successful, AI technology has the potential to overcome many of the barriers currently faced in these diverse disease areas.

8.1. Integration of Multi-Omics Data

In this chapter, we will examine the application of agentic AI in drug discovery, including a high-level overview of how AI is addressing some of the previously mentioned drug development challenges. This chapter will conclude with a discussion on multi-omics data integration as it is relevant to drug development. The digital health revolution is greatly facilitated by multi-omics, a comprehensive approach that combines the analysis of genomic, proteomic, and metabolomic data, among other types of data. This technology allows machine learning methods, particularly neural networks, to analyze integrated data in neglected problems such as designing de novo drugs or investigating specific molecular systems often influenced by environmental conditions. Besides, it also formalizes personalized medicine based on genomics, proteomics, environment, and lifestyle data in different therapeutic areas, including rare and neurological diseases. The extensive nature of multi-omics data provides a more in-depth knowledge of the entire disease and physiological, or therapeutic mechanisms based on the functions of different biological levels.
Integrating data from diverse sources assists in the discovery of things unseen using a single or dual modality-based study, leading to a more in-depth understanding of patients' phenotypes as well as how they respond to treatment. Multi-omics data yield mathematical features that are used to train deep learning models capable of detecting important clinical correlations and relevant hidden patterns in an agnostic way. High-dimensional multi-omics data are often heterogeneous in both kind and range. These data, once combined, develop a state-of-the-art approach to combine not only an optimal range of types but also more features for data-driven precision and personalized medicine. The technical problem in multi-omics data is critical to its success. Therefore, we will concentrate specifically on merging multi-omics data because addressing smaller data volumes and leakage between various data forms can lead to simpler, slower, and less generalizable system assumptions. Future work should focus on the exploration of the multi-omics data combination problem. More significantly, based on the patient characteristics and error distribution, the subsequent step investigates the adaptability and configurability of leveraging the agentic AI models.

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