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Application of artificial intelligence to thyroid diseases and their management

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Abstract:
Artificial intelligence (AI) is transforming healthcare and offers new tools in clinical research, personalized medicine, and medical diagnostics. Thyroid function tests represent an important asset for physicians in the diagnosis and monitoring of pathologies. Artificial intelligence tools can clearly assist physicians and specialists in laboratory medicine to optimize test prescription, test interpretation, decision-making, process optimization, and assay design. Our article is reviewing several of these aspects. As thyroid AI models rely on large data sets, which often require distributed learning from multi-center contributions, this article also briefly discusses this issue.

Keywords: artificial intelligence; biomarkers; clinical decision support systems; digital health; thyroid diseases

Introduction

The thyroid is a crucial endocrine organ in the human body. Thyroid cancer, one of the most prevalent endocrine system malignancies, accounts for the largest proportion of head and neck cancers. [1] It consists of two connected lobes and is one of the largest endocrine glands in the human body, weighing 20–30 g in adults. Thyroid lesions are often found on the gland, with a prevalence of 4–7%. Most of them are symptomatic, and thyroid hormone secretion is normal. [2] Thyroid cancer (TC) is a common malignant tumor of the head and neck. The incidence of malignant tumors is seventh, ranked fourth in the incidence in women. [3] The histologic types can be divided into papillary carcinoma and Papillary Thyroid Carcinoma (PTC), Follicular Cancer, Medullary Cancer, and Undifferentiated cancer. PTC is the most common one, accounting for 80–88%. [4]

The term artificial intelligence (AI) was first used in 1956 by John McCarthy, who used his work on neural networks to solidify the orientation of the field. [5] Artificial intelligence (AI) is a field of computing science mimicking the human thought processes and behaviors used to make decisions or take actions [6]. It uses different mathematical and algorithmic approaches, from operational research to constrained programming [6]. Artificial intelligence is transforming healthcare and offers new promising solutions in clinical examination, precision medicine, research, and clinical diagnostics [6–9]. The expectations associated with AI are growing exponentially as the volume of medical data available (electronic medical records, laboratory informatics systems, omics, mobile health applications, *etc*.) is constantly increasing [10]. In the field of laboratory medicine, automation and digitalization are stimulating the use of AI and the evolution of laboratory services [7–8]. Artificial intelligence also allows disorders and outcome forecasts based on routine laboratory analysis and understanding of complex biochemical information [11].

Since its inception, many industries have integrated artificial intelligence into their work environments. The healthcare sector mainly uses natural language processing to drive the conceptualization and classification of clinical documents. [12] Learning algorithms can improve precision and accuracy when interacting with training information. Such programming allows humans to better understand disease diagnosis, care procedures, rehabilitation variability, and patient outcomes. According to Hamet and Tremblay, AI in medicine comprises two domains: the virtual domain involves informatics approaches, while the physical domain encompasses the robots used to conduct procedures. [13] Understanding the association between AI and medicine is vital to learning the benefits and shortcomings.

AI provides numerous advantages in healthcare over traditional approaches since it enhances the analytical process and the techniques to facilitate decision-making. Additionally, the topic of explainable AI or interpretable AI is growing in popularity, as it is reasonable to foresee that AI will be an integral part of the future of the medical field. Computer-based programs using AI have been successfully used in many applications related to the brain, breast, and lung. [14-16] Learning algorithms can improve precision and accuracy when interacting with training information. Such programming allows humans to better understand disease diagnosis, care procedures, rehabilitation variability, and patient outcomes. According to Hamet and Tremblay, AI in medicine comprises two domains: the virtual domain involves informatics approaches, while the physical domain encompasses the robots used to conduct procedures. [13] Understanding the association between AI and medicine is vital to learning the benefits and shortcomings. AI provides numerous advantages in healthcare over traditional approaches since it enhances the analytical process and the techniques to facilitate decision-making. Additionally, the topic of explainable AI or interpretable AI is growing in popularity, as it is reasonable to foresee that AI will be an integral part of the future of the medical field. Computer-based programs using AI have been successfully used in many applications related to the brain, breast, and lung. [14-16]

Thyroid hormones are fundamental for development, neuronal growth, fertility, and metabolism [1]. Thyroid diseases are frequent conditions, affecting millions of people around the world, related to multiple health problems, and for which thyroid function tests (TFT) are frequently ordered for the diagnosis and monitoring of diseases [18]. The main aim of this study is to review some of the potential applications of AI in thyroid function tests.

Material and Method

The application of AI to thyroid disorders: preliminary observations from radiology and imaging

The complexity of the diagnosis of some thyroid pathologies has stimulated the development of AI solutions to assist physicians. Different examples coming from the fields of radiology and imaging can illustrate this trend. A first observation is that using AI-based computerized diagnosis systems can personalize and optimize the management of thyroid nodules. Because of clinical requests to diminish superfluous fine needle aspiration (FNA), AI-based solutions have been proposed as ways of expanding the exactness of ultrasonography-based conclusions for less-experienced administrators and to address the intricacy of the fragmented risk stratification systems [19].

A second observation is the possibility of staging malignancy of thyroid tumors and how deep learning AI models can help to differentiate between malignant tumors and benign thyroid tumors based on distinctive clinical and ultrasonographic characteristics [20]. Artificial intelligence algorithms have been utilized for the classification of thyroid nodules utilizing ultrasound pictures, cytopathology pictures, and molecular markers [21]. Interestingly, the accuracy of the AI model was superior to that of radiologists for diagnosing malignancy and was leading to significant reduction of FNA [19]. Published data showed that neural network precision in segregating advanced *versus* non-advanced thyroid carcinomas was 84%, with positive and negative predictive values of 87% and 92%, respectively [22].

The use of AI to determine tumor classification is also an important step in the choice of an optimum treatment [21]. A third observation is the application of AI for the automation of image analysis with whole-slide imaging [23]. A recent study reported that the coefficients of correlation with manual evaluation were higher than 0.76 and that the diagnosis performance of the AI-based robotized models was similar to a specialist pathologist analysis [23].

The application of AI to laboratory medicine: considerations for thyroid function tests

Thyroid function tests represent an important asset for physicians in the diagnosis and monitoring of thyroid pathologies. Artificial intelligence applications have the potential to optimize correct test prescription, test interpretation, decision-making, process optimization, and assay design (Figure 1). We will discuss some of these perspectives at the pre-analytical, analytical, and post-analytical levels.

Impact on preanalytical factors and process optimization

An important aspect of the preanalytical phase is the appropriate test ordering by physicians. Guiding the physicians in the ordering of the right TFT according to clinical context is important, especially in a context where the overuse of TFT has been documented in both hospital and primary care practices [24]. The optimal choice of TFT is important to make effective clinical decisions and to help physicians spend more time treating patients [25]. In contrast, excessive TFT ordering policies can cause financial strain in a period of rising medical care costs. Artificial intelligence-based companions have the potential to help physicians optimize TFT prescriptions and define intelligent order sets that can contribute to reducing laboratory overutilization [24]. A recent study investigated the value of a deep learning-based automated system to recommend appropriate laboratory tests [25]. The AI-based model achieved a higher area under the receiver operating characteristics curve (AUROC micro = 0.98 and AUROC macro = 0.94). The integration of such an AI companion into existing workflows can reduce under- and over-utilization of TFT [26]. Clinical laboratories are still in important phases of consolidation and automation, with emphasis also placed on the preanalytical levels and sample transportation. Clinical laboratories also constantly work on the improvement of patients' experiences and laboratory services. Artificial intelligence can possibly upgrade all degrees of testing work processes and test assortment, including work process enhancement and operational efficiency [27–28]. Artificial intelligence tools can also have applications to assist medical teams with matrix selection at the time of tube collection, recommendations of an adequate moment for sampling, and the integration of variables to control and monitor the transportation of samples.

Impact on the analytical phase

Improvement of TFT assays remains an objective for the clinical community and for scientific societies [28]. The standardization is also still ongoing from the perspective of better commutability of results and clinical cut-off points between laboratories [29]. However, several challenges are still paving the way, and the use of AI for the *in silico* design of TFT assays can offer an additional solution to go forward [30]. *In silico* modeling can enhance the know-how of TFT assays and technology capabilities with perspectives of increased efficiency and robustness of assays, reduction of time-to-market, and streamline of operations and production. *In silico* approaches can be applied to immunoassays for epitope prediction, the simulation of optimized assay sequences and formats, and the validation of novel proofs of concept at the bioprocessing level. Additionally, as TFTs are still prone to interference with consequences for patients, as up to half of recorded thyroid obstructions prompted misdiagnosis or potentially unseemly administration, including the remedy of a superfluous treatment, the *in silico* design can significantly decrease the sensitivity to interfering compounds and improve TFT assays [32].

Impact on the post-analytical phase

The definition of personalized reference intervals is important for the appropriate use of TFT. The use of data mining and AI approaches can help clinical laboratory teams establish or verify reference intervals for TFT by extracting and integrating data from laboratory informatic systems and electronic medical records [32]. A large amount of data can be processed, and reference intervals can be more accurately adjusted to different population subgroups.

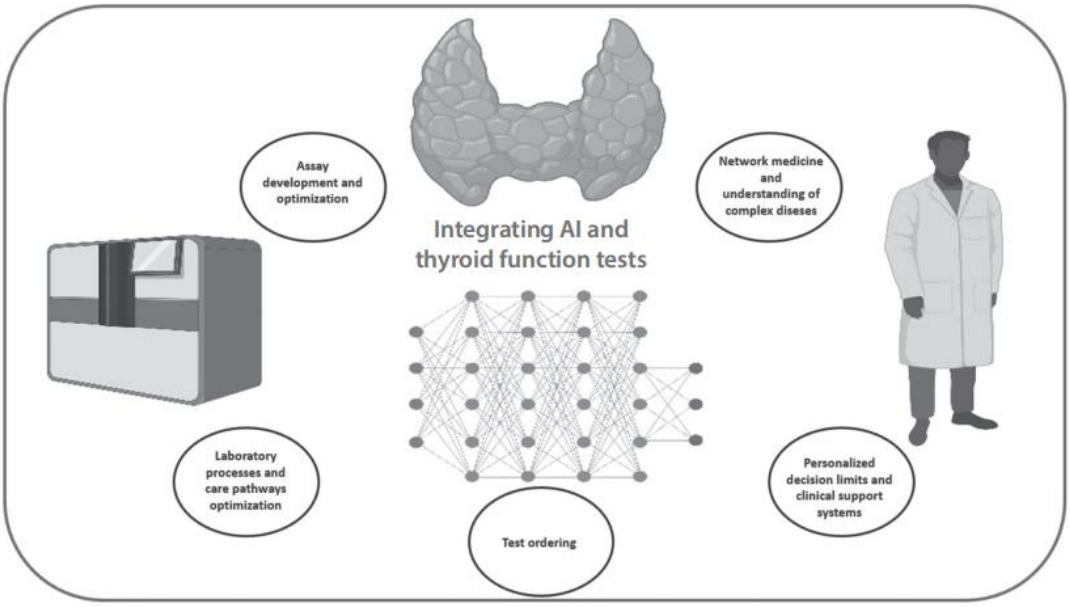

Figure 1. The perspectives associated to the integration of AI and thyroid function tests.

Thyroid function test variability within and between subjects is high with the example of TSH concentrations, which can change over the long run inside a person because of different internal and outer elements [33]. Artificial intelligence tools could also be seen as additional options to better estimate and derive biological variability by diving into clinical databases to identify sources of fluctuations for TFT and therefore adjust the decision limit accordingly [34]. Recent data showed that AI and machine learning methods might offer unique insight into the complex hypothalamic-pituitary-thyroid axis, identify factors determining individual TSH concentration, and may be relevant tools that guide us in making appropriate therapeutic decisions for the individual patient [35].

Clinical decision support systems

Clinical decision support systems (CDSS) are designed to utilize medical data, knowledge, and analysis engines to generate patient-specific assessments or recommendations to health professionals in order to assist in decision-making [36]. Artificial intelligence can enable CDSS to aid the decision-making process for thyroid diseases through an intelligent component. The building of CDSS for the interpretation of TFT and image signals will provide integrated approaches to support clinical decisions regarding thyroid diseases and the integration of clinical practice guidelines. Clinical decision support systems using machine learning-evaluated geometric and morphological features have already been evaluated for the classification of thyroid nodules [37]. The COVID-19 pandemic also triggers the development of CDSS using imaging techniques and biomarkers for mortality prediction [38]. The same strategy could be applied to thyroid cancer, using the progress of AI to separate and break down morphological, textural, and molecular features [39]. Clinical decision support systems might help physicians accelerate the decision-making process for thyroid diseases. Another example is the potential use of AI-based CDSS for diagnosis and estimating the risk of the development of thyroid autoimmune disease [40]. Using AI-based CDSS for potential autoimmune thyroid pathobiology will rely on the integration of complex datasets coming from genetic (human leukocyte antigen (HLA) and other genes), environmental (different triggers (viruses, microbes), and immune system characteristics (autoantibodies, cytokines) [41–42]. This could be particularly relevant to distinguishing different types of thyroid autoimmune diseases, such as autoimmune thyroiditis, Hashimoto thyroiditis, Hashimoto disease, or Grave disease, with different patterns of hyperthyroidism or hypothyroidism. The application of AI in autoimmune diseases in most recent studies has focused on patient identification, hazard expectation, finding, disorder subtype, evolution, and complications [40]. A diagnosis solution based on an artificial immune recognition system with balanced preprocessing is one of the most promising future methods for evaluating thyroid diseases [41].

Challenges and additional perspectives Challenges

In order to achieve the clinical benefits of using AI for thyroid pathology and for optimized use of TFT, several challenges must be considered [43]:

- Establish a comprehensive legal framework for AI and update existing relevant legislation to ensure that it is fit for purpose.
- Identify and promote best practices ensuring the robustness of big data and AI systems in the health sector, both at the stages of development and actual use, to reduce potential biases and errors in AI-based decision-making.
- Improve data interoperability and support the development of data infrastructure, with the goal of providing reliable flow data with standardized formats, the necessary cybersecurity provisions, and data protections.
- Support the development of national electronic health records and improve the interoperability of health data.
- Stimulate scientific research and development in the field to boost the updates of AI applications in healthcare and support patient access to the best available technologies.
- Equip the workforce with the necessary skill sets to maximize the positive impact of AI and conduct a comprehensive regulatory assessment of the medical profession's frameworks to determine whether they are fit for the use of patient-centered AI in healthcare provision.
- Ensure that AI is applied with full respect to data protection rules while observing the balance between scientific advancement and patient protection.

- Put in place mechanisms to ensure educational assistance for patients to allow them to better understand and use AI and empower them to actively participate in the management of their health.
- Define the value and business models around AI tools and carefully assess the benefits in terms of clinical outcomes, patient experience, and costs.
- Encourage the active involvement of healthcare work forces in the construction and validation of AI solutions and decision support systems.

Continuous learning in secure multi-centric coalitions

Although recent research results have shown effective and promising results obtained by AI models for diagnosis, classification, and clinical decision support for the treatment of thyroidal disorders, the deployment of these models must adapt to the variability of data acquisition across clinical environments. Therefore, the use of continual learning models that adapt to local clinical practices must be triggered. Such models should be promoted within coalitions of hospitals sharing the same practices and guidelines. A solution to provide efficient, reliable, and privacy-preserving distributed learning inside a coalition of hospitals has been previously described. [44]

Network medicine

Thyroid pathology encompasses a heterogeneous group of clinical-pathological entities [39]. Network medicine offers the possibility to integrate multiomics data with very well-characterized clinical phenotypes to work on the comprehension of complex diseases [45]. Using AI to apply network medicine to thyroid pathobiology will rely on the integration of complex datasets coming from hyperspectral mass spectrometry imaging, from the molecular signatures of thyroid tumors, from proteomic analysis, and from transcriptomes or other multi-omics networks [46–48]. The combination of AI and network medicine will contribute to a superior comprehension of thyroid disorders and the improvement of upgraded diagnostic and treatment options by eliciting causal relationships in the biological continuum, from molecular omics data to histology [49].

Conclusion

Artificial intelligence is becoming a useful tool to assist in the in the diagnosis and risk classification of thyroid diseases. Artificial intelligence companions can significantly improve the performance of clinical laboratories for process optimization as well as provide support for clinical decisions. Artificial intelligence tools offer *in vitro* diagnostic companies' novel options for the design and improvement of TFT. The incorporation of AI into clinical pathways also offers opportunities to enhance care. Pathways, laboratory tests, prescriptions, clinical diagnosis, and patients' outcomes. In the context of network medicine, AI will help to better understand complex thyroid diseases, detect molecular mechanisms, and develop potential new treatment strategies.

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