finds the best solutions to a problem by mimicking biological evolution — to develop a library of serves for the system to use.

The second noteworthy aspect of the AI-based system was the role of humans in its development. In table tennis, players serve by tossing the ball up before striking it with the racket. Ace's tosses were based on human demonstrations, adapted to the robot's motional features so that the final serve adhered to the official rules of the game. Expert players informed the genetic algorithm, determining which of the possible serve strategies were challenging enough to be used. If, during training with a human coach, a particular serve succeeded at least 95% of the time across 20 attempts, it became part of the robot's serve set.

Ace played against five elite and two professional players (Fig. 1), beating three of the elite players. It lost to both professional players, winning one game out of seven in the matches played against them. Ace's performance was mainly due to its ability to generate different kinds of spin and its consistency in returning the ball, rather than the use of faster-than-human shots. This is noteworthy, because it might have been expected that specialized machines capable of generating extremely high speeds would rely predominantly on power. The authors report that Kinjiro Nakamura, a table-tennis player who competed in the 1992 Barcelona Olympics, commented as he watched Ace perform a particular shot: "No one else would have been able to do that. I didn't think it was possible. But the fact that it was possible … means that there is a possibility that a human could do it too."

Overall, the authors report a successful implementation of a fast-acting AI-based system that operates in a real environment. It must be stressed, however, that Ace relied on guidance and assessment from humans who understood the situations and interactions involved in table tennis. Nevertheless, it is remarkable that human specialists such as Nakamura might learn new skills just by playing against and observing Ace, suggesting that AI-controlled robotic systems could be an arena for human development beyond table tennis.

In 1997, the chess-playing system Deep Blue defeated world champion Garry Kasparov in a six-game match[6]. Ace has yet to reach the equivalent level of performance, and even if it were capable of beating a world-champion table-tennis player, the system is far from being humanoid. For example, unlike human players, it observes the game from multiple points at once. AI-based chess engines can now be run using a mobile phone rather than the specialized computer required for DeepBlue — as autonomous systems become more advanced, Ace might also one day become outdated. Nevertheless, like Deep Blue, Ace is an important milestone, showcasing the potential of the next generation of high-quality, competitive agents that interact with physical environments.

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Immunology

A healthy thymus predicts lifelong health

Graham Anderson

It was thought that the thymus serves its purpose for the immune system early in life. Insights about the organ in adults reveal its importance for later well-being. **See p.986 & p.995**

The thymus is an organ in the chest that produces T cells, essential components of the immune system[1,2]. However, after peaking in size in adolescence, the thymus progressively shrinks as people age, leaving its relevance to adult health unclear. In two papers in *Nature*, Bernatz *et al.*[3,4] present an artificial-intelligence approach for assessing the health of the thymus in adults. The authors identify thymic health as an indicator of healthy ageing and of whether immunotherapy for cancer treatment is likely to be successful.

In the immune system, the thymus supports the development of functional T cells from progenitor cells in the bone marrow. For immune responses to be effective, T cells must recognize protein fragments called antigens that are presented on other cells by molecules that form part of the major histocompatibility complex. To avoid unwanted responses to the body's own cells (as happens in autoimmune disorders), T cells must discriminate between antigens that are derived from host (or self) cells and foreign cells. The processes that enable T-cell discrimination between self and non-self antigens occur in the thymus in microenvironments consisting of thymic epithelial cells (TECs) and antigen-presenting immune cells called dendritic cells[5].

> **"The authors provide a tantalizing glimpse of the functional role of the adult thymus."**

Thymus function is not constant throughout a person's life. The organ reduces in size with age through a process called thymic involution. This typically begins in childhood and involves the loss of the microenvironments that support T-cell development, resulting in diminished T-cell production in older people[6,7]. Consequently, the key time frame of thymic function is typically associated with newborn and juvenile periods of life — the T cells that are produced at these times then serve the immune system in adulthood. However, evidence has emerged that surgical removal of the thymus has a detrimental effect on adult health[8], pointing to the need to re-evaluate the role of this organ after childhood.

In one of their papers (page 986)[3], Bernatz and colleagues developed a deep-learning AI framework to analyse computed tomography (CT) images of the chest from more than 5,000 individuals (Fig. 1). The region of the image showing the thymus was used in an AI-based data analysis to create a thymic 'health score' associated with the size of the organ. This ranged from zero (maximal thymic involution, meaning low thymic health) to one (the highest level of thymic health). The authors used this system to analyse thymus images from two large groups of people being monitored in two clinical settings: the US National Lung Screening Trial (NLST, which has data for more than 25,000 people) and the Framingham Heart Study (FHS; more than 2,500 participants).

By correlating thymic health score with

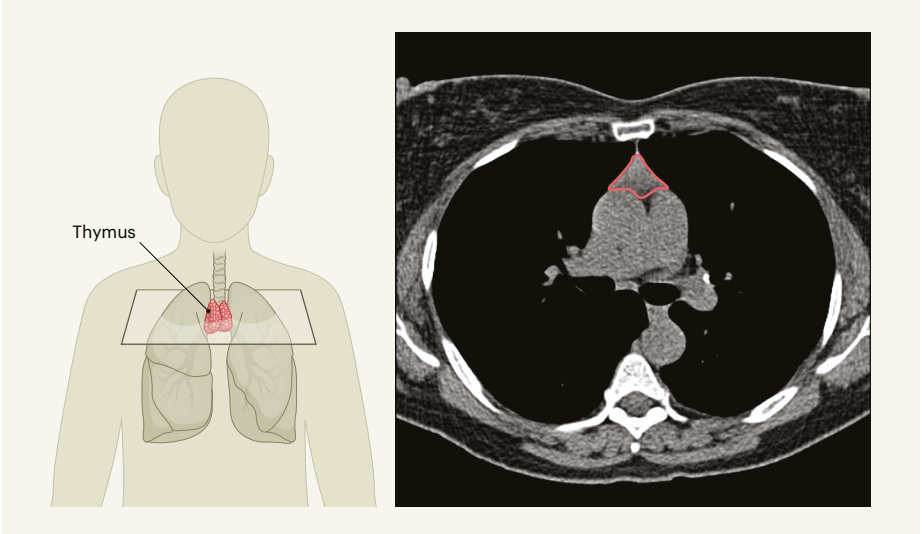

Figure 1 | Assessing the thymus in adults. Bernatz *et al.*[3,4] examined the relationship between an organ called the thymus and disease susceptibility and responses to cancer treatment in adults. The authors analysed the organ's size as a way to assess its health, using scans called computed tomography (CT) images (left panel shows the thymus position and the angle of the CT cross-section through the body; right panel shows an example CT image with a large thymus outlined in red). Having a larger thymus correlated with better health and better immunotherapy outcomes. (Adapted from Fig. 1 of ref. 3.)

information about the health of the specific individual, the authors made several key observations. Thymic health was lower in men than in women, and showed evidence of age-related decline. This provided the authors with an indicator of the robustness of their AI-based deep-learning framework. Analysis of the NLST data identified people with higher thymic health scores as having a reduced incidence of lung cancer. Mortality for other types of disease — including those of the heart, digestive system and lung, as well as metabolic disorders such as diabetes — were also lower in people with higher thymic health scores.

Using the FHS data to consider thymic health in relation to lifestyle choices and chronic inflammation, the authors found that people with high levels of proteins associated with inflammation (such as IL-6) had a lower thymic health score. Alcohol consumption had no correlation with thymic health, whereas smoking was associated with poor thymic health. The authors therefore conclude that thymic health varies between individuals, has predictive value for various diseases and can be influenced by some lifestyle choices.

In the other paper (page 995)[4], Bernatz *et al.* went further with their thymic health-score approach and related it to measurements of thymus function and responsiveness to cancer treatment. People who had not yet received cancer treatment and who had higher thymic health scores had higher levels of an indicator called a T-cell-receptor excision circle, which is a marker of T cells being produced in the thymus. Furthermore, high thymic health scores correlated with reduced disease progression and mortality for many types of cancer, including breast, kidney and melanoma.

Thymic health scores were analysed in relation to responses to immunotherapy for cancer treatment, and this provided evidence that thymic health might be a way to identify people who are most likely to benefit from such treatment. The authors suggest that thymic health could be used to predict the outcome and success of treatment for various forms of cancer.

The decline in thymus function with age is well described[9], and such evidence supports the idea that the adult thymus has only a minor, if not insignificant, role in the health of an individual. In Bernatz and colleagues' work, the people studied included those at stages of life well after the onset of thymic involution. The authors' studies are useful because they provide evidence that there is a link between adult thymus health, disease susceptibility and treatment success.

Some key questions remain unanswered. Is thymus size directly responsible for improvements in lifelong health? Or is the presence of a healthy thymus simply an unrelated indicator of the overall health of an individual? Because thymic ageing involves loss of the epithelial-cell microenvironments that support T-cell production, more work will be needed to examine whether thymus size in humans is a valid marker of the availability of TECs that support T-cell production.

Mouse models have shown that reversing thymic involution and increasing TEC availability enhances immune responses in aged mice[10]. Furthermore, accumulation of age-associated TECs (atypical cells associated with tissue degeneration) occurs in the aged mouse thymus, which might hinder thymus function[11]. The effect of age-associated TECs in the human thymus, their relevance to thymic involution and their relationship to thymus size warrants further investigation.

Bernatz and colleagues' reliance on the use of thymus size as a way to assess its function is worth noting in terms of considering limitations to their studies. For example, the presence of two anatomically distinct regions of the thymus — known as the cortical and medullary thymic areas — are essential to support T-cell development. However, analysis of these areas is not possible in the type of CT images used in the authors' studies. Furthermore, although TECs decline with age, thymic fat (adipose) tissue increases[6,7]. Consequently, measurements of overall thymus size would not reveal changes in cell types occurring in the tissue.

Moreover, it remains to be investigated how various attributes of the thymus, such as size, relate to subtle yet key aspects of the organ's function. These include the generation of functionally distinct sub-lineages of T cells, and the establishment of tolerance to self-antigens. Bernatz *et al.* provide a tantalizing glimpse of the functional role of the adult thymus, and suggest that the use of image-based thymic assessment might offer a way to monitor healthy ageing and predict individual responses to disease treatment.

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