

# Optimal robot for intervention for individuals with autism spectrum disorders

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With recent rapid advances in technology, human-like robots have begun functioning in a variety of ways. As increasing anecdotal evidence suggests, robots may offer many unique opportunities for helping individuals with autism spectrum disorders (ASD). Individuals with ASD often achieve a higher degree of task engagement through the interaction with robots than through interactions with human trainees. The type and form of robots to be used for individuals with ASD have been meticulously considered. Simple robots and animal robots are acceptable because of their simplicity and the ease of interesting and engaging interactions. Android robots have the benefit of the potential of generalization into daily life to some extent. Considering the affinity between robots and users is important to draw out the potential capabilities of robotic intervention to the fullest extent. In the robotic condition, factors such as the appearance, biological

motion, clothes, hairstyle, and disposition are important. Many factors of a user, such as age, sex, and IQ, may also affect the affinity of individuals with ASD toward a robot. The potential end-users of this technology may be unaware or unconvinced of the potential roles of robots in ASD interventions. If trainers have extensive experience in using robots, they can identify many potential roles of robots based on their experience. To date, only a few studies have been conducted in the field of robotics for providing assistance to individuals with ASD, and future studies are needed to realize an optimal robot for this purpose.

**Keywords:** *affinity, android robot, autism spectrum disorder, potential role, simple robot.*

<http://onlinelibrary.wiley.com/doi/10.1111/pcn.13132/full>

## Background

The core symptoms of autism spectrum disorders (ASD) are social communication challenges and restricted repetitive behaviors. It is estimated that approximately 1 in 54 children has ASD in the USA, based on the Autism and Developmental Disabilities Monitoring Network (Arizona, Arkansas, Colorado, Georgia, Maryland, Minnesota, Missouri, New Jersey, North Carolina, Tennessee, and Wisconsin).<sup>1</sup> In the USA, \$2.4 million is the estimated cost of supporting an individual with ASD during his or her life span<sup>2</sup>; this poses a social problem.

Many interventions exist for individuals with ASD. An evidence-based study<sup>3</sup> demonstrated that developmental intervention was effective for individuals with ASD. However, many individuals with ASD cannot easily sustain high motivation and concentration for intervention by humans.<sup>4</sup> Intensive sensory processing in individuals with ASD may be affected by the dynamic facial features and expressions of human beings, which are likely to induce sensory and emotional overstimulation and distractions.<sup>5</sup> This can, consequently, interfere with their learning as they tend to actively avoid the sensory stimulations and instead focus on more predictable elementary features. A critical need to establish novel and effective support tools and therapeutic intervention strategies specific to individuals with ASD must be addressed.

With recent rapid advances in technology, human-like robots have functioned in a variety of ways, including eye contact, nodding, and touching. Robots are actively employed in various fields, such as nursing, education, and medical care. Many people have a sense of curiosity and security toward robots. Robots are expected to do jobs that people originally performed and jobs that people cannot perform.

## Superiority of Robots over Humans for ASD

There is increasing anecdotal evidence of the fact that individuals with ASD may have unique opportunities to use robots for help.<sup>6–10</sup> Robots allow them to control and replicate a scene with smooth and accurate conversation, despite their reaction, contributing to a more structured and standardized intervention. Unlike human beings, robots that operate within predictable and lawful systems provide a highly structured learning environment to individuals with ASD, helping them to focus on relevant stimuli. Structured interactions with humanoid robots are likely to form standardized social situations in which certain social behaviors can occur.<sup>11,12</sup>

Individuals with ASD often achieve a higher degree of task engagement through interactions with robots than through interactions with human trainees.<sup>4,8,11–14</sup> Specifically, their task engagement is better when facing a robot than when facing a human.<sup>14–17</sup> In general, the affinity of humans to another person is stronger than that to artificial objects. For individuals with ASD, however, neither preference

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bias toward humans<sup>18</sup> nor repulsion toward artificial objects (in contrast to real humans) is observed.<sup>8</sup> In some instances, they show behaviors toward robots that individuals without ASD have toward humans.<sup>19</sup> Furthermore, an intervention for individuals with ASD requires long-term patience; therefore, a robot can perform consistently, which is a great advantage. In the field of autism, an attempt to apply robotics has been made for the following target processes: assisting the diagnostic process, improving eye contact and self-initiated interactions, turn-taking activities, imitation, emotion recognition, joint attention (JA), and triadic interactions.<sup>6,9,20</sup> A previous study<sup>21</sup> indicated carryover effects after job-interview training by using an android robot. In that study, with a 1-year follow-up after the intervention, at least half of the participants had been employed after passing job-interview examinations. Considering that individuals with ASD have an affinity to robots, many other ways seem to exist for using robots for an intervention.

Robots have a variety of stimulus elements. For example, Kumazaki *et al.*<sup>22</sup> suggested that gaze, voice volume, nodding, and facial expressions (e.g., smiling, nodding, and brow movements) are potential stimuli. It is difficult to determine which stimulus is stronger. Anzalone *et al.*<sup>23</sup> performed a JA test and reported that multimodal JA induction (i.e., gazing, pointing, and vocalizing) was more efficient than lower levels of stimulation in participants with ASD and in participants with typical development, suggesting that higher levels of stimulation are better than lower levels of stimulation. 'Higher levels of stimulation' can be defined as more complex interaction from robots, such as multimodal stimulation (e.g., gazing and pointing, gazing and touching). 'Lower levels of stimulation' can be defined as simpler interaction from robots, such as sole stimulation (e.g., gazing only, pointing only, touching only).

It was proposed that a variety of robots could be used in therapeutic interventions for individuals with ASD,<sup>6,9,10</sup> although optimal robots must be selected depending on the content of the intervention. To select an optimal robot, considering the preference of robots by individuals with ASD is also important. Other important viewpoints may exist for selecting an optimal robot. Identifying the optimal type of robots is necessary for the success of an intervention. This review

will focus on the diverseness of robots and will investigate optimal robots for an intervention for individuals with ASD.

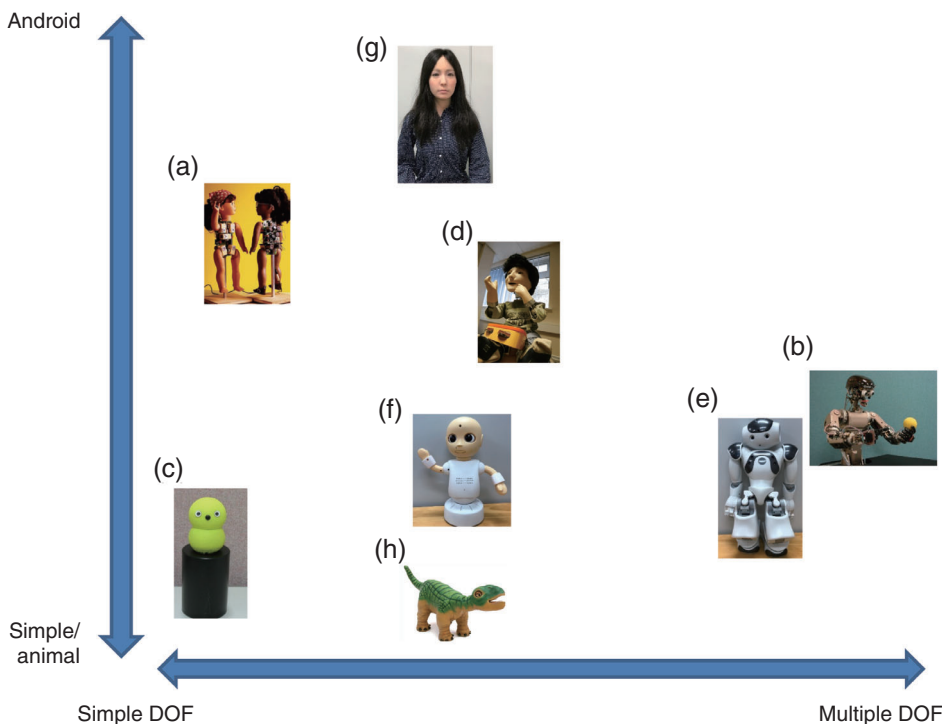
## Main Robots in the Field of ASD

First, persons interacting with a robot are often impressed by the robot's physical appearance and motion. The robot's appearance (various levels of anthropomorphism, such as humanoid, animal-like, and machine-like; i.e., nonbiomimetic systems and the fidelity of the reproduction) ranges from stylized features to a realistic and complex appearance. They are impressed not only by its physical appearance but also by its various levels of biological motion. Specifically, a more human-like impression is received from a robot that can move its arm with multiple degrees of freedom (DOF) in the shoulder than from a robot that can move its arms only up and down in a single plane of motion.

Contrary to use for elderly people, robots oriented for physical interaction, such as stuffed animal types (e.g., PARO, National Institute of Advanced Industrial Science and Technology, Tokyo, Japan)<sup>24</sup> and huggable types (e.g., Telenoid, Osaka University, Osaka, Japan)<sup>25</sup> have rarely been used and reported in the clinical research field of ASD. In this paper, we introduce famous robots in the field of autism research, with a special focus on physical appearance and motion.

## Robota

Robota<sup>26,27</sup> (Fig. 1a; height, 45 cm; weight, 500 g) is a doll-shaped robot. Its body consists of LEGO parts (Lego Group, Billund, Denmark) and plastic components of a commercial doll. The robot possesses five DOF: one in each arm and leg, and one in the neck. It was developed as one of the first humanoid robots to be used in therapeutic interventions for individuals with ASD. It can react through passive motion of its limbs and head and through saying its name and describing its behavior. A previous study<sup>26</sup> reported that repeated exposure to Robota results in an improvement in basic social interaction skills (e.g., imitation, turn-taking, and role-switching) and communicative competence in children with ASD (age, 5–10 years).



**Fig. 1** The main robots used in the field of autism therapy, based on their location on the android-to-simple/animal spectrum and on simple degrees of freedom (DOF) to multiple DOF. (a) Robota (from Ricks and Colton<sup>9</sup>). (b) Infanoid (courtesy of H. Kozima). (c) Keepon (courtesy of H. Kozima). (d) KASPAR (from Robins *et al.*<sup>26</sup>). (e) NAO (image courtesy of the authors). (f) CommU (image courtesy of the authors). (g) Actroid-F (image courtesy of the authors). (h) Pleo (from Kim *et al.*<sup>45</sup>).

### Infanoid

Infanoid<sup>29</sup> (Fig. 1b; height, 48 cm; weight, 15 kg) is an upper-torso humanoid. It does not have any skin (i.e., it is an exposed machine). It has two hands (four fingers and a thumb in each hand) and two eyes (with two different-colored charge-coupled device cameras for peripheral and foveal view). It possesses 29 DOF – seven DOF in the head, three DOF in the neck, six DOF in each arm (excluding the hands), two DOF in each hand, and three DOF in the trunk – which produce lifelike and human-like movements. It allows attentive and emotional interaction with humans through gaze, pointing, and facial expressions. A previous study<sup>29</sup> revealed that the repeated interaction of a child with ASD (age, 6 years) with Infanoid promoted the child's ability to naturally enter a social loop.

### Keepon

Keepon<sup>30,31</sup> (Fig. 1c; height, 25 cm; weight, 898 g) is a little yellow snowman-shaped robot. It has a soft, yellow rubber body with two beady eyes, and a black nose. Four motors control the driving of four DOF to make its body lean from side to side and from front to back, bob up and down, and pan or rotate on its base. A touch mode reacts to human touches and a dance mode dances in synchronized rhythm with music. A previous study<sup>31</sup> revealed that interaction of children with ASD (age, 2–4 years) with Keepon promoted their performance of triadic interpersonal interactions.

### KASPAR

KASPAR<sup>32–34</sup> (Fig. 1d; height, 60 cm; weight, 15 kg) is a child-sized humanoid robot. Its face consists of a silicon-rubber mask. It possesses 17 DOF – nine DOF in the head and neck and four DOF in each arm. It has the ability to not only move its torso, arms, and head but also to open and close its mouth and eyes. A restricted range of movements causes KASPAR to 'minimize' its emotional expressiveness so that it is uncomplicated and easy to interpret. It is capable of responding to the touch of individuals as well as moving its arms, head, and eyes. A previous study<sup>33</sup> revealed that the interaction of children with ASD (age, 6–8 years) with KASPAR promoted better collaboration and cooperation with a partner.

### NAO

NAO<sup>4,23,28,35,36</sup> (Fig. 1e; height, 58 cm; weight, 4.3 kg) is a child-sized humanoid robot; its body consists of plastic skin. It has 25 DOF (four DOF for the joints for each arm, two DOF for each hand, five DOF for each leg, two DOF for the head, and one DOF to control the hips). It is able to capture substantial information about the environment by using multimodal sensors, such as cameras, microphones, and tactile sensors. It can speak, and a certain degree of nonverbal communication can be ensured owing to its wide motility and its luminescent eyes. Previous studies have revealed its potential to improve JA in children with ASD (age, 2–4 years),<sup>4</sup> and to reduce the percentage of stereotyped behavior in children with ASD (age, 5–13 years).<sup>28</sup>

### CommU

CommU<sup>15,16,37–39</sup> (Fig. 1f; height, 30 cm; weight, 740 g) is a child-sized humanoid robot and is characterized by having clearly distinguishable eyes. Its body surface is made of plastic. It has 14 DOF as follows: two DOF for the waist, two DOF for each shoulder, three DOF for the neck, three DOF for the eyes, one DOF for the eyelids, and one DOF for the mouth. CommU is the successor model of M3-Synchy,<sup>40,41</sup> which has the same 13 DOF, except for the eyelids, as well as the following four DOF: one DOF for each elbow and two DOF for wheels to move around. The CommU design is safer than that of M3-Synchy in that CommU has a smooth round body shape without gaps among body parts that could pinch fingers, and it has a dislocation mechanism in the shoulder to avoid the breaking of motors when a user applies force to its arms. M3-Synchy and CommU first appeared in 2010 and 2015, respectively, in press

releases. The careful design of the eyes and multiple DOF of CommU are dedicated to controlling the direction of the eye gaze. It has the capability of shifting its gaze and blinking. Smooth movement and positioning of its eyelids allow the determination of a range of simplified expressions that are less complex than those of a real human face. Previous research has revealed its potential to promote self-disclosure in adolescents with ASD (mean age, 15.91 years),<sup>14</sup> and to improve JA in children with ASD (age, 5–6 years).<sup>3</sup>

### Actroid-F

Actroid-F<sup>22,42–44</sup> (Fig. 1g; height, 165 cm; weight, 30 kg), a female type of humanoid robot, has an appearance similar to that of a real person. The skin is composed of silicone. It has 12 DOF: seven DOF for the face (two DOF for the eyes, two DOF for the eyebrows, one DOF for the eyelids, one DOF for the mouth, and one DOF for the cheeks), three DOF for the neck, one DOF for the shoulder, and one DOF for waist. Actroid-F was first described in a 2010 press release. It is possible to generate blinking, breathing, gaze, and head movements. Its operation is also possible by a remote conversation system (e.g., teleoperation). During speech, it can also incorporate changes in facial expression (e.g., smiling, nodding, and brow movements). A previous study<sup>22</sup> demonstrated its potential to promote individuals with ASD (18–27 years old) to understand the importance of nonverbal communication.

### Pleo

Pleo<sup>32,45</sup> (Fig. 1h; height, 17.8 cm; length, 50.8 cm) is a pet dinosaur robot. It has a realistic layer of artificial skin. It has 14 DOF with customized gears and force-feedback, thereby allowing tail-wagging, neck-positioning, mouth and eyelid control, and a slow walking movement. Small and large speakers are installed in the jaw and just above its tail, respectively. Owing to a camera-based vision system for light detection and navigation as well as microphones, touch sensors, ground foot sensors, force-feedback sensors, and an orientation tilt sensor for body positioning, the robot can move autonomously and is capable of expressing emotions by motions and sounds in response to an interactor's touch or various interactions, such as caresses or giving food. A previous study<sup>45</sup> revealed that the interaction of children with ASD (age, 4–12 years) with Pleo facilitated social interaction with another person and elicited social behavior during interaction.

## Potential of Simple Robots and Animal Robots

The type and form of robots used in interventions for individuals with ASD have been meticulously considered. Each type of robot has advantages and disadvantages in such interventions. A less lifelike appearance might allow for a physical appearance that exaggerates social cues or helps focus attention on particular social cues that are necessary for social-skill training with limited distracting or confusing stimuli. A variety of simple robots are used in an intervention for individuals with ASD.

Which robot should be selected varies, depending on the aim and types of intervention. For example, in facilitating JA, a robot should have clear eyes and the ability to turn its eyes. Eye contact, which is often lacking in children with ASD, is required as a basic social skill, so the clear eyes of a robot help with recognizing and interpreting communication signals in these children and are expected to facilitate JA. However, a robot's inability to turn its eyes is a limitation in terms of its similarity to a human agent. In the context of these factors, CommU, which has clear eyes and can turn its eyes, may be the most suitable robot for facilitating JA.

In social-skill training for children to facilitate the understanding of emotional recognition, facial expressions of robots must be less complex than those of real human faces. When children with ASD look at someone else's face, they feel that the information contained in the human face is overwhelming.<sup>5</sup> The robot's simple face enables children with ASD to pay attention to it without feeling the anxiety

and sensory overload they often experience around humans. Given these factors, KASPAR, a simple robot that can show a variety of expressions, seems to be one of the most suitable robots for social-skill training to teach emotional recognition.

PLEO's expressiveness, versatility, and pet-like appearance may attract ASD children with a severe autistic trait. When they see something with a human form, they are often withdrawn and tend to avoid interactions. Animal-like robots do not trigger such reactions, and they can focus on these robots.

These animal-like robots have advantages in their simplicity and the ease of interesting and engaging interactions; however, they may not be generalized because of a large difference between their appearance and the appearance of another person.

### Potential of Android Robots

Because android robots are beneficial in terms of the similarity to humans, they may be generalized more easily.

The potential application of android robots has been shown in interventions for individuals with ASD. Kumazaki *et al.*<sup>22</sup> developed a job-interview training program using an android robot (Actroid-F). In their study, individuals with ASD received the training and underwent a mock job interview with a human interviewer before and after the training. Their nonverbal communication skills and self-confidence improved, and the levels of salivary cortisol were significantly decreased after the training, compared to those in the control group.

Yoshikawa *et al.*<sup>44</sup> investigated whether interacting with an Actroid-F would increase the frequency or duration of eye contact and whether these interactions would be maintained after ceasing the intervention. In their study, adolescents with ASD participated in consecutive sessions of a semi-structured conversation; they alternately faced a human female or a female-type android robot interlocutor. They revealed that the adolescents tended to look more at the eyes of the human as they repeated the interaction.

The findings of the above two studies have shown that android robots can potentially simulate daily life to some extent; however, neither has provided evidence that the acquired skills can be incorporated for a long time after the intervention. Whether an intervention using an android robot contributes to the acquisition of communication skills in addition to long-term generalization in daily lives remains uncertain. The question is still waiting for new experiments.

### Affinity Between Robots and Individuals with ASD

Individuals with ASD have strong likes and dislikes<sup>46</sup>; therefore, considering the affinity between robots and users is important to draw out the potential abilities of a robotic intervention to the fullest extent. Some studies indicate which robot goes well with individuals with ASD.

Kumazaki *et al.*<sup>40</sup> evaluated the impact of robot appearance on the preferences of 17 individuals with ASD (age, 10–17 years) by using an android (i.e., Actroid-F<sup>43</sup>), a mascot (i.e., smile supplement robot<sup>47</sup>), and a mechanical robot (i.e., M3-Synchy<sup>41</sup>). In that study, each participant completed a sequence of three interactional sessions using the android, mascot, and mechanical robots in a random order. After the interaction, a human interviewer asked participants, 'Which robot did you like most?' and 'Which was the second-best one?' Contrary to their expectations that individuals with ASD would prefer the plainer and obviously robotic robots (i.e., mascot or mechanical robot), they found that individuals with more severe autistic traits had a significant preference for the android robot.

Kumazaki *et al.*<sup>17</sup> assessed three technological agents (i.e., simple humanoid robot [CommU<sup>37</sup>], android robot [Actroid-F<sup>43</sup>], and screen-based digital avatar) and humans for eliciting a response to a social cue in children with ASD (age, 1–7 years). In their study design, the three technological agents and the human assistant, in a random order, provided the verbal social bid of 'Hey!' In addition, the child's response to each social bid was measured

offline by counting the frequency with which the child turned his or her head and/or eyes toward the agent. The individuals with ASD responded more often to a simple humanoid robot than to an android robot or human.

Moreover, Kumazaki *et al.*<sup>15</sup> evaluated personal disclosures of events with specific emotional content for individuals with ASD (average age, 15.91 years) across two different robotic systems (android robot [Actroid-F<sup>43</sup>] and simplistic humanoid robot [CommU<sup>37</sup>]) and human interactions. All participants completed a sequence of three interaction conditions in a random order. To evaluate their enjoyment level, a self-report survey was conducted on a 9-point Likert scale at the end of the session. Audio recordings were collected during the experimental session and after the interaction the research team transcribed them and totaled the number of words used in each exchange (i.e., amount of self-disclosures) between the participant and agent across various conditions. Therefore, adolescents with ASD acquired not only higher levels of enjoyment via conversing with the visually simple robot but also a greater level of self-disclosure with the visually simple robot, compared to a human. Adolescents with ASD did not show higher rates of self-disclosure with the android robot.

These studies highlight the reality that not all types of robotic interactions will go well with an individual with ASD. To increase treatment efficiency, seeking an optimal combination of affinity between the robotic condition and the characters of users is needed.

### Optimal Robotic Condition for Individuals with ASD

The physical appearances of robots currently used as therapeutic tools for these individuals are highly varied.<sup>9</sup> Therefore, both robot developers and therapists wish to identify the optimal appearance of robots used in interventions. It is generally believed that some individuals with ASD are likely to prefer a more robotic appearance and behavior.<sup>9</sup> There is another study<sup>40</sup> indicating that individuals with a higher autistic trait prefer an android robot. Here, what is important may not be 'simple is better' but 'simpler than humans is better.' Kumazaki *et al.*<sup>40</sup> suggested in their study that one reason why individuals with ASD strongly prefer an android robot may be explained by the advanced technology used to create it. The other reason is its resemblance to adults because individuals with higher autistic traits did not prefer the 'Baby Schema robot.'<sup>48</sup> Therefore, various factors may be involved in robot preference of individuals with ASD.

For the success of a robotic intervention, other viewpoints may be important, in addition to selecting the optimal robot. Huijnen *et al.*<sup>49</sup> suggested that, even if the same robot is used, the clothes and hairstyle of the robot across different contexts and roles need to be chosen. In addition, Huijnen suggested the need to change the voice, length of sentences, and talking speed. Other than these factors, real-time response and so forth seem to be important factors for the success of a robotic intervention. Moreover, establishment or limitation of realism is possible by varying levels of biological motion.

A robot's disposition is also important for therapy.<sup>50</sup> The distance from the robot to a user affects the user's impression of it. A reasonable distance differs, depending on each individual. If robots can move around in their environment and are not fixed to a physical location in which users do not have anxiety, the therapy will proceed smoothly. However, few mobile robots are available in interventions for individuals with ASD. The development of new mobile robots is expected.

### Influential Factors of Users for the Success of a Robotic Intervention

Affinity between robots and users may also be determined by many factors of the users. The ideal age for using each robot in therapy is not clear. As assumed from our preliminary study, younger users may prefer a robot that has a short stature and a simple appearance.



Sex perception of the robot and gender identity of an individual with ASD may be considered when a humanoid robot is used for targeted, individualized social therapy strategies aimed at facilitating interactions and maximizing beneficial effects. In general, typically developed adults rate a robot of the opposite sex as more trustworthy, engaging, and credible than a robot matching the sex of the individual.<sup>51</sup> Whether this finding is relevant to individuals with ASD has not been clarified. Further studies are needed to determine the optimal sex of a robot to portray to individuals with ASD.

Pioggia *et al.*<sup>52</sup> suggested that individuals with lower IQ cannot obtain much benefit from robotic therapy. However, Kozima *et al.*<sup>30</sup> suggest that very simple robots (e.g., Keepon) are very helpful, even for individuals with ASD whose IQs are low. Therefore, various factors, including age, sex, and IQ, may be involved in robot preference of users. In addition, other important factors, such as social skills, communication skills, social anxiety, and depression, should be considered. The selection of robots for interacting with this population should be determined carefully to take into account these factors, which may expand the potential of robotic intervention. Individuals with ASD have difficulty adjusting to new circumstances (i.e., staying with an unfamiliar robot); therefore, showing a movie of the robot may be helpful before initiating the actual therapy sessions. The amount of exposure they have to a robot affects the quality of interaction between individuals with ASD and the robot. The first response offered by the child to the robot as a stimulus may differ from that elicited by the child after becoming familiar with the robot. The perspective that the relationship to a robot may change after repeated interaction with the robot is also important.

### Importance of Being Aware of the Potential Roles of a Robotic Intervention by Clinicians

To date, a growing number of studies have been reported on human–robot interaction in individuals with ASD. Although most of these findings are promising, advances in robot-mediated interventions are still minimal, and there is less progress regarding their clinical applicability.<sup>53</sup> The potential roles of robots in interventions for individuals with ASD may not be recognized by the potential end-users of this technology, such as individuals with ASD, their caregivers, and clinicians.<sup>7,8</sup> Few users initially have experience in using robots. To acknowledge the potential roles of robots used in interventions for individuals with ASD, it is important for users to have the opportunity to experience using a robot.

Huijnen *et al.*<sup>54</sup> recruited care and/or educational professionals and used the KASPAR robot for individuals with ASD to investigate the roles, strengths, and challenges of robot-mediated interventions. The following six roles of the robot were identified by the care and/or educational professionals: provoker, reinforcer, trainer, mediator, prompter, and diagnostic information provider. The professionals provided an overview of requirements for the robot, end-user, environment, and practical implementation. They conducted an important study, although their study has limitations in that their participants had never experienced using robots for an intervention before the research. If trainers have much experience in using robots, they can identify other potential roles of robots, based on their experience. Further study is needed that target trainers who have much experience in using robots.

### Conclusion

The affinity to robots by individuals with ASD is promising and robots are possible therapeutic tools for interventions for these children. A variety of robots exist, and their appearance and biological motion range across many levels of anthropomorphism. Android robots could be mostly generalized in daily life. Simple robots may allow for a physical appearance that exaggerates social cues or helps focus attention on particular social cues, which are helpful for training by limiting distracting or confusing stimuli. Due to the varied preferences of individuals with ASD, identifying the preference for

robots is necessary for the success of intervention. Robotic preference varies, depending on the situation that they face with a robot. Many factors of users, such as age, sex, and IQ, may also affect the affinity toward a robot by individuals with ASD. To date, the studies conducted in this area are insufficient. Future studies are needed to clarify the optimal robot for individuals with ASD.

### Acknowledgments

This study was partially supported by Grants-in-Aid for Scientific Research funded by the Japan Society for the Promotion of Science (19H04880) and the Center of Innovation Program funded by the Japan Science and Technology Agency.

### Disclosure statement

The authors have no conflicts of interest to declare.

### Author contribution

H.K. undertook the literature search, and wrote the manuscript under the supervision and feedback of T.M., Y.Y., Y.M., H.I., M.K., T.S., and M.M.; H.K. formulated the overall design and objectives of the manuscript.

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