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## Strategic Outlook toward 2030: Japan's research for allergy and immunology – Secondary publication

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1 Review Article

2 **Strategic Outlook toward 2030: Japan's Research for Allergy and Immunology**

3

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97 **Abstract**

98 *Strategic Outlook toward 2030: Japan's Research for Allergy and Immunology*

99 (*Strategy 2030*) is the national research strategy based on Japan's Basic Law on

100 Measures Against Allergic Diseases, a first of its kind worldwide. This strategy was

101 established by a multi-disciplinary committee consisting of administrators of the

102 Ministry of Health, Labour and Welfare of Japan, young and senior experts from

103 various research societies and associations, and representatives of patient and public

104 groups. Whereas the issues of transition, integration, and international collaboration

105 have yet to be solved in this research realm in Japan, identification of unmet needs,

106 digitization of information and transparent procedures, and strategic planning for

107 complex problems (a process dubbed *MIERUKA* by the Toyota Way) are crucial to

108 share and tackle the same vision and goals. The committee developed three specific

109 actions focusing on preemptive treatment, interdisciplinarity and internationality, and

110 life stage. The real success of *Strategy 2030* is made by the spontaneous contributions

111 of doctors, dentists, veterinarians, and other medical professionals; basic and clinical

112 research scientists, research supporters, and pharmaceutical/medical device companies;

113 manufacturers of food, healthcare, and home appliances; and patients, their families,



114 and the public. The hope is to establish a stable society in which people can live long,  
115 healthy lives, as free as possible from allergic and immunological diseases, at each  
116 individual life stage. This article is based on a Japanese review first reported in *Arrerugi*,  
117 introduces the developmental process and details of *Strategy 2030*.

118

119 **Keywords:** allergy, immunology, Japan, MHLW, strategy

## 120 **Abbreviations**

121 ABPM: Allergic Bronchopulmonary Mycosis

122 AERD: Aspirin-exacerbated Respiratory Disease

123 AI: Artificial Intelligence

124 AMED: Japan Agency for Medical Research and Development

125 CIRB: Central Institutional Review Board

126 DiHS: Drug-induced Hypersensitivity Syndrome

127 EMA: European Medicines Agency

128 FDA: Food and Drug Administration

129 HFSP: Human Frontier Science Program

- 130 IRUD: Initiative on Rare and Undiagnosed Diseases
- 131 J-RDMM: Japanese Rare Disease Models & Mechanisms Network
- 132 MEXT: Ministry of Education, Culture, Sports, Science and Technology, Japan
- 133 MHLW: Ministry of Health, Labour and Welfare, Japan
- 134 PMDA: Pharmaceuticals and Medical Devices Agency
- 135 PPI: Patient and Public Involvement
- 136 R&D: Research and development

137 **Introduction**

138 Should Japan proceed with research on allergy and immunology, despite the increase in  
139 social security costs and the decrease in tax revenue following the progress of the  
140 super-aged society? If yes, from what perspective should the research be promoted? To  
141 address these questions, we planned and formulated *Strategic Outlook toward 2030:  
142 Japan's Research for Allergy and Immunology* (hereinafter, *Strategy 2030*) focusing on a  
143 process dubbed *MIERUKA*. It was originally a management technique used at Toyota to  
144 increase efficiency and effectiveness by making the steps more visible<sup>1</sup> and is now used  
145 in a broader sense. Herein, we defined *MIERUKA* as the identification of unmet needs,  
146 digitization of information, making the process transparent, and strategic planning for  
147 complex problems, toward safe societal development.

148 Japan has a long history of studying allergic and immunological diseases.  
149 Countermeasures instituted by the Japanese government were launched nearly half a  
150 century ago, and the national research project regarding childhood asthma treatment was  
151 first conducted in 1972.<sup>2</sup> Since then, the Ministry of Health, Labour and Welfare, Japan  
152 (MHLW) has played an essential role in tackling these major societal problems, and the

153 Basic Law on Measures Against Allergic Diseases (hereinafter, the “basic law”) came  
154 into force in June 2014,<sup>3</sup> and the Basic Guideline for Promoting Measures Against  
155 Allergic Diseases was announced in March 2017.<sup>4</sup> These pioneering national efforts are  
156 quite indispensable because one out of two people in Japan still have some form of  
157 allergic and/or immunological disorders.<sup>5</sup> Patients with these diseases show long-lasting  
158 phenotype(s), often repeating exacerbations and remissions, and with potential fatality,  
159 such as, anaphylaxis and severe drug hypersensitivity.

160 In addition, the “cross-sectional” problem lies in the measures against the diseases  
161 of which symptoms occur in various organs including the eyes, ears, skin, nose, kidney,  
162 respiratory organs, gastrointestinal organs, and central nervous system. Multiple different  
163 departments must thus be involved in the examination of patients, meaning that the close  
164 communication necessary for producing high-level study results is somewhat hard to  
165 achieve. Another hurdle for allergic and immunological diseases is the “vertical”  
166 problem concerning allergic march, a characteristic state in the progression and transition  
167 of various allergic diseases. Departments that examine these patients will change over  
168 time along with their growth and symptoms, and consequently, cohort-type studies are  
169 quite hard to accomplish. Furthermore, data and sampling methods for “big data”

170 analysis have not been standardized, domestic cooperation is currently insufficient, and  
171 international harmonization is almost nonexistent. Due to differences in the  
172 characteristics of patients with allergic and immunological diseases between Westerners  
173 and Asians,<sup>6</sup> research and development (R&D) results presented in the European and  
174 North American literature must be applied carefully to clinical practice in Japan.

175 Thus, we shaped our vision focusing on *MIERUKA* for the unmet needs and  
176 complex issues across different levels and miscellaneous stakeholders through national  
177 and international collaborative research, based on which effective measures could be  
178 taken for the society in which patients and public live long, healthy lives, at each  
179 individual life stage. We set three goals for doctors, dentists, veterinarians, and other  
180 medical professionals (nurses, pharmacists, nutritionists, and clinical laboratory  
181 technicians); basic and clinical research scientists, supporting research staffs, and  
182 pharmaceutical/medical device companies; food, healthcare, and home appliance  
183 manufacturers; and patients, their families, and the public to promote their active  
184 participation and spontaneous contribution. The basic law also stated the responsibilities  
185 of these stakeholders, who will be a large driving force.<sup>3</sup> Finally, to achieve the vision  
186 and goals, major actions are to be promoted with three key words: Preemptive Treatment,

187 Interdisciplinarity and Internationality, and Life Stage. This review introduces the  
188 developmental process and details of *Strategy 2030*. This article is based on a Japanese  
189 review first reported in *Arrerugi*.<sup>7</sup>

190

### 191 **Developmental process and characteristics of *Strategy 2030***

192 To plan this *Strategy 2030* holistically and effectively, it was essential to precisely  
193 understand the state of the art and to prioritize globally extracted keywords and themes.

194 The MHLW played a central role in specially organizing a planning group with its  
195 grant-in-aid and with cooperation from seven relevant academic societies: the Japanese

196 Society of Allergology, the Japanese Society of Pediatric Allergy and Clinical  
197 Immunology, the Japanese Dermatological Association, the Oto-Rhino-Laryngological

198 Society of Japan, the Japanese Ophthalmological Society, the Japanese Respiratory  
199 Society, and the Japanese Society for Immunology (Figure 1). Two physicians/scientists

200 were nominated from each society as collaborators of the planning group. As a general  
201 rule, these nominations included one from the professorial level (around the age of 55

202 years) and one from the emerging scientist level (around the age of 45 years), for

203 continuous follow-up over the next 10 years. A research consortium including these  
204 research collaborators created the first report (Figure 1).

205       Based on the convergence of domestic and foreign wisdom, the vision and three  
206 goals were established to perform three major actions (Figure 2) and to promote  
207 spontaneous contributions by various national and international stakeholders in the  
208 industry, academia, government, and public. To accelerate the achievement, the MHLW  
209 founded the Investigative Commission to clarify the positioning of the strategy, collect  
210 opinions from patients, their families, and the public (Figure 3), and finalized this  
211 *Strategy 2030*<sup>8</sup>, including 12 specific actions (Figure 4), a first of its kind worldwide.

212

213 **Actions I: Fundamental research for pathophysiological elucidation and innovative**  
214 **preemptive treatments**

215 A fundamental platform for understanding and stratifying the diversity of allergic and  
216 immunological diseases is essential to facilitate efficient preemptive treatment for  
217 appropriate targets. Particularly, as recent microbiome research has revealed, it is an  
218 effective strategy for identifying novel targets for diagnosis and treatment, to focus on  
219 the relationship between external factors and host factors at interfaces such as the

220 epidermis and mucosal surface. Cooperation across organs, specialized fields, and  
221 medical departments, and collaboration with engineering, science, agriculture, etc. will  
222 be promoted as well (Figure 4).

223

224 **I-1. Fundamental research for understanding and stratification of disease diversity**

225 Allergic and immunological diseases have a variety of phenotypes and disease states,  
226 depending on the age of onset, severity, and prognosis. Thus, the natural course,  
227 responsiveness to standard therapy, and the rate of side effects vary greatly among  
228 studies on these diseases, and the reported findings are often irreproducible. Thus,  
229 stratification should be performed from a comprehensive perspective, including detailed  
230 phenotype analysis (deep phenotyping)<sup>9</sup>, and an analysis of endotypes based on an  
231 understanding of the molecular network, rather than uniform biomarkers (endotyping).<sup>10</sup>

232 During the process, it becomes necessary to standardize the diagnostic criteria and  
233 classification rule among different institutions to help advance research on  
234 pathophysiology and evaluate treatment efficacy. In addition, stratification of healthy  
235 individuals (selecting high-risk groups of “potential patients”) is also required to  
236 implement precision medicine<sup>11</sup> and preemptive therapy, which will be described in the



237 next section. Furthermore, the utilization of artificial intelligence (AI) in “big data”  
238 analysis and standardizing phenotypes in model organisms need to be promoted.

239 A large-scale birth cohort study under the Japan Environment and Children’s  
240 Study<sup>12</sup> and a third-generation cohort study by the Tohoku Medical Megabank  
241 Organization<sup>13</sup> are currently being conducted in Japan. Stratification of patients based on  
242 phenotypes is being attempted by bringing together such clinical information databases.

243 However, these approaches pose many problems regarding differences in information  
244 categories, terminology, diagnostic definition, or the completeness of the stored  
245 information. Thus, in collaboration with Action III-4 described later, it is indispensable  
246 to make full use of good practices in the rare disease realm, where national and  
247 international databases have been harmonized in a globally standardized format,<sup>14</sup>  
248 resulting in the confirmed diagnosis, treatment and medical care.<sup>15,16</sup> With the

249 standardization of clinical information and the deep phenotyping of patients with allergic  
250 and immunological diseases, multi-omics analysis of their samples from the peripheral  
251 blood, skin, and airway lesions, etc. would be promoted greatly. On the other hand, it is  
252 impossible to perform such multi-omics analyses in a single research laboratory or

253 institution. Thus, the use of preexisting programs and closer cooperation among  
254 laboratories/institutions are essential.

255

256 **I-2. Preemptive treatment R&D for future practical implementation of precision**

257 **medicine**

258 Whereas personalized medicine is a concept in which the best treatment method would  
259 be provided for each individual patient requiring high medical expenses, precision  
260 medicine groups patients into subpopulations who present the same specific symptoms,  
261 or those who are expected to respond to drugs in the same manner.<sup>11</sup> Treatment methods  
262 or disease prevention will be established for and delivered to each subgroup in precision  
263 medicine, with higher expected cost efficiency. Globally, many precision medicine  
264 initiatives have been launched to identify patient subpopulations for many  
265 immune-related multifactorial diseases.<sup>11,17-20</sup> However, these strategies have not clearly  
266 focused on specific patient populations. Thus, Action I-2 toward the regulatory approval  
267 of novel medical drugs and devices has to be promoted in collaboration with Action I-1,  
268 where subpopulations will be clearly determined by “screening” methods such as deep

269 phenotyping or endotyping within patient populations or within a group of healthy  
270 individuals.

271       The approach of our country toward the practical use of disease multi-omics  
272 profiles the patients for early diagnosis, optimal treatment, and quick/precise prognosis  
273 and is generating many possibilities regarding preemptive therapy. It has been shown,  
274 for example, that the combination of thorough treatment of atopic dermatitis and early  
275 introduction of potential allergens is effective in preventing food allergies.<sup>21</sup> In addition,  
276 dysbiosis of the skin flora is reported to be involved in the onset of atopic dermatitis.<sup>22</sup>  
277 Amelioration of dysbiosis combined with strengthening of the barrier at the interface  
278 between the organism and the external world (e.g., skin, eyes, nose, and mouth) is  
279 expected to be important for preventing the onset of other immunological disorders that  
280 may follow. These measures may become key developmental strategies for preemptive  
281 therapy against allergic march. A recent study also suggested that anti-IgE antibody  
282 administration during pregnancy could lead to the development of allergy.<sup>23</sup>

283       Still, several difficulties in conducting academic research remain to be addressed in  
284 the development phase based on collaboration with pharmaceutical and medical device  
285 companies. Such difficulties include delayed timing for joining global clinical trials. It

286 is necessary to clarify good practices for academic-industry collaborative R&D and its  
287 societal implementation when proceeding with Action I-2. Cooperation with Action II-3  
288 described later is also needed for the effective utilization of a framework for conducting  
289 multicenter clinical trials in Japan and overseas.

290

291 **I-3. Fundamental research focusing on the correlation between host and extrinsic**  
292 **factors**

293 For stratification, which is essential for preemptive treatment R&D, it is important to  
294 elucidate the interaction between host factors, including immunological and genetic  
295 backgrounds, and various extrinsic factors at the interface. It has been reported that  
296 dysbiosis of the skin<sup>22</sup> or respiratory tract, smoking, exposure to air pollution and small  
297 particulate matter (PM<sub>2.5</sub>), and susceptibility to specific viruses play important roles in  
298 the onset, progression, and increased severity of allergic and immunological  
299 diseases.<sup>10,24-26</sup> Of note, comparison of two groups of people (the Amish and Hutterites)  
300 who share a similar genetic background revealed that the risk of asthma was lower  
301 among the group that engaged in traditional farming compared to those who engaged in  
302 modernized farming.<sup>27</sup> In this case, the natural immune responses differed according to

303 external factors (here, differences in farming style). Such studies with a new approach  
304 that incorporate external factors are gaining much attention and are to be encouraged.  
305 Making the most of the relatively homogeneous genetic background of the Japanese  
306 population, Action I-3 would promote comparisons and investigations of the diversity  
307 regarding lifestyle, weather, or seasons toward future breakthroughs.

308       Given the importance of results regarding locality- or age-related differences, data  
309 sharing and coordination with research using existing specimens and cohort studies are  
310 also essential. On-going studies conducted on donated blood samples stored by the  
311 Japanese Red Cross Society have revealed the regional and generational diversity of the  
312 allergen(s)-specific IgE positivity rate.<sup>28</sup> Furthermore, collaborative research involving  
313 housing, bedding, home electronics, food, beverage, and cosmetics manufacturers will  
314 be effective not only for creating a healthier internal environment of the body, but also  
315 for controlling external allergens (such as cedar pollen) where one often needs political  
316 measures as well.<sup>29</sup> Particularly, collaboration with Actions III-1 and III-2 focusing  
317 research on patients' life stage is of importance for comparison of generational  
318 differences.

319

320 **I-4. Interdisciplinary R&D for multi-organ system network**

321 Despite having many aspects in common regarding immunological mechanisms,  
322 neurological findings (for symptoms such as itching),<sup>30</sup> and barrier functions,<sup>31</sup> various  
323 symptoms in different organs have prevented interdisciplinary R&D regarding the  
324 multi-organ system network beyond the medical department boundaries in Japan.  
325 Several countries set up their registration systems for individual diseases at the national  
326 level, and many epidemiological study results that utilized such databases have been  
327 reported.<sup>32</sup> Furthermore, it is important to collect objective data that may be useful  
328 within different clinical fields and to standardize the data for furthering research that  
329 goes beyond the borders of individual organs. For example, asthma is often diagnosed  
330 subjectively via auscultation among doctors, although the findings must be transformed  
331 into objective data.<sup>33</sup> Such interactions between different fields will be essential for  
332 driving forward R&D beyond the borders, which would be promoted by Action I-4, in  
333 collaboration with Action I-3 for improving the environment inside and outside the  
334 body; Action II-2 for investigative R&D for unmet medical needs utilizing apps,  
335 wearable devices, and AI; and Action II-4 for international cooperation and human  
336 resource development.

337 Of note, many advanced results on allergic and immunological research have been  
338 reported as a result of information sharing from basic to clinical research. In addition to  
339 promoting translational research, a future issue will be how to proceed with “reverse  
340 translational research”, which links questions arising in daily clinical practice to basic  
341 research. Thus, building a sustainable collaborative platform is extremely important in  
342 reference to pioneering strategies in the rare disease field described later in Action III-4.

343

344 **Actions II: Cross-sectional research related to effective promotion and societal**  
345 **development**

346 Effective promotion of allergic and immunological research requires the establishment  
347 of cross-sectional infrastructure that incorporates new perspectives and new participants.

348 Actions II focus on four areas: patient and public involvement (PPI), *MIERUKA* of  
349 unmet needs, clinical research infrastructure including central ethics review, and  
350 promotion of international collaboration (Figure 4).

351

352 **II-1. Bidirectional research promotion via patient and public involvement**

353 Since the 2000s, a system has been established so that patients and related patient  
354 organizations and civil society groups could participate in the design, conducting, and  
355 reporting of clinical studies in several countries including the UK.<sup>34</sup> It has been  
356 increasingly understood that designing clinical trials with patient input is useful for  
357 improving the quality and speed of research.<sup>35</sup> In these discussions, the importance of  
358 their active participation in research has become clear, apart from the issues on subject  
359 protection. It was also clarified that it is important to educate groups that cover multiple  
360 diseases rather than focus on a single disease (area).<sup>36</sup> Action II-1 aims to clarify the  
361 appropriateness of the PPI in Japan's allergic and immunological research for the study  
362 design, execution, and report of clinical research and trials in the platform promoted by  
363 Action II-3.

364 In the realm of allergy and immunology in Japan, the PPI is insufficient compared  
365 to other pioneering realms, including cancer and rare disease. However, some patient  
366 and public organizations with statuses of general incorporated associations or non-profit  
367 organizations are actively engaged in providing appropriate medical information and  
368 providing patient education in cooperation with healthcare professionals.<sup>37</sup> There is a  
369 need for an information network in which appropriate information is quickly transmitted



370 to the public, not only for lifestyle management including clothing, food, and shelter,

371 but also for PPI.

372

373 **II-2. Investigative R&D for unmet medical needs of allergy and immunology**

374 Unmet medical needs for allergic and immunological research include the discrepancy

375 between clinical guidelines and on-site medical care, the accurate prediction of the start

376 date of pollen scattering, the optimization of disease and complication management, and

377 the establishment of team medical care.<sup>38,39</sup> It has also been pointed out that it is

378 difficult to evaluate the results of research on allergic and immunological diseases

379 because of poor indicators for objectively evaluating disease activity and life

380 satisfaction. Furthermore, it is necessary to investigate these medical and social needs

381 comprehensively and evaluate them together with host and external factors of patients;

382 otherwise, the *bona fide* unmet medical needs cannot be identified.<sup>40-43</sup>

383 To verify the future effects of *Strategy 2030*, Action II-2 would promote research to

384 create indicators of *MIERUKA* for disease activity and life satisfaction. To this end, in

385 connection with Actions I-4 and II-4, it is desirable to work with diverse stakeholders,

386 including industries, to develop apps and wearable devices that can comprehensively

387 collect data regarding patient needs, as well as to promote the utilization of AI  
388 technology. It is also important to promptly reflect the needs of patients detected by  
389 such collaboration between industry, academia, government, and private sectors into  
390 basic/clinical/policy research.

391

392 **II-3. Effective utilization of the clinical research platform for allergy and**

393 **immunology**

394 Multicenter clinical studies/trials are considered the gold standard method for recent  
395 medical evaluation. With increasing size and complexity of the research, the burdens on  
396 institutional review boards (IRBs) and on clinical investigators seeking IRB review  
397 increases. Thus, review by the centralized IRB (CIRB) is being promoted worldwide to  
398 facilitate rapid patient-centered ethics reviews. This review is aimed at guaranteeing  
399 coherence of reviews in observational studies in which multiple institutions participate,  
400 and to avoid inconsistent reviews based on ethics decisions that are not in line with  
401 actual clinical practice. In the United States, collective review has become obligatory  
402 under the revised Common Rule.<sup>44</sup> Collective review has also been obligated in the UK  
403 since 2004 based on the EU Clinical Trial Directive /Regulations.<sup>45</sup> In Japan, a

404 collective review is permitted in the Ethical Guidelines for Medical and Health  
405 Research Involving Human Subjects<sup>46</sup> and in the Ethical Guidelines for Human  
406 Genome/Gene Analysis Research.<sup>47</sup> Standardization of review quality and improvement  
407 of the efficiency of the review are being developed via smooth implementation of the  
408 CIRB.

409 Currently, to accelerate high-quality clinical research indispensable to the  
410 development of innovative pharmaceuticals and medical devices from Japan, Core  
411 Clinical Research Hospitals, which play a central role in national and international  
412 clinical research and in investigator-initiated clinical trials are being developed, to also  
413 provide the necessary support for other medical institutions.<sup>48</sup> Regarding allergic and  
414 clinical disorders, the maintenance of medical provision systems is being promoted in  
415 each jurisdiction, to establish the allergic disease medical core hospitals.<sup>49</sup> Action II-3  
416 will actively collaborate with and effectively utilize the CIRB in these core hospitals to  
417 promote the preemptive treatment R&D in Action I-2.

418

419 **II-4. International collaborative research promotion fostering a diverse next**

420 **generation**

421 It has been reported in recent years that the pathophysiology of allergic and  
422 immunological diseases may differ between Europeans and Asians.<sup>6</sup> Thus, study results  
423 presented in European and North American literature must be applied carefully to  
424 clinical practice in Japan. Also, in the Japanese medical system, medical specialists see  
425 patients from the beginning, unlike in Europe or North America, where general  
426 practitioners play a central role in primary care. An accurate diagnosis and precise  
427 approaches to patients with specific diseases are generally guaranteed at a very early  
428 stage in our system. However, such differences between Japan and other countries are  
429 not sufficiently disseminated in the English language to the international community.  
430 Lack of information on the current state of Japan, including disease prevalence, poses  
431 some risk that may make it difficult for Japan to engage smoothly in international  
432 collaborative research or clinical trials. Furthermore, the number of internationally  
433 co-authored papers with high impact from Japan has been relatively declining, as  
434 reported by the Shibayama Initiative of the Ministry of Education, Culture, Sports,  
435 Science and Technology, Japan (MEXT).<sup>50</sup>

436       Herein, Action II-4 would promote the construction of a sustainable platform  
437 fostering scientists who will bridge Japan and other countries and play an active part in

438 the world without bias regarding age, sex, or ethnicity to increase the international  
439 presence of Japan. Academic societies would lead these efforts beyond their borders,  
440 especially in forming a task force composed of emerging researchers. Global human  
441 resource exchange and international collaborative research will be promoted between  
442 universities and research institutions with such a platform, so that young scientists  
443 would actively participate in international programs such as the Human Frontier Science  
444 Program (HFSP)<sup>51</sup> and the Interstellar Initiative presented jointly by the AMED and the  
445 New York Academy of Sciences.<sup>52</sup> Needless to say, it is also important to strengthen the  
446 dissemination of information in English on the state-of-play of allergic and  
447 immunological research, development, and medical care in Japan.

448

449 **Actions III: Key research focusing on allergic and immunological disease**

450 **characteristics such as those in different life stages**

451 One of the most important characteristics of allergic and immunological diseases is that  
452 the disease and condition change with the transition from the mother to the baby, infant,  
453 adolescent, adult, and elderly. In addition, it is necessary to focus on research regarding  
454 severe, intractable, and refractory diseases and on those with a small number of patients.

455 Zeroing “preventable deaths” in some severe allergic and immunological diseases is a  
456 key goal of *Strategy 2030*, aimed at optimizing medical care and disseminating  
457 preventive and therapeutic methods according to these disease characteristics.

458

459 **III-1. Pediatric and transitional research on allergy and immunology focusing on**  
460 **mother-child associations**

461 Allergic and immunological diseases are thought to be a result of complicated  
462 interactions between genetic predisposition and epigenetics reflecting environmental  
463 factors, including those that occur during gestation. Particularly, environmental factors  
464 pertaining immediately after birth; feeding practices, including breastfeeding and  
465 weaning; and the development of skin barrier function in early infancy that affects skin  
466 sensitization are all likely to affect life-long allergen sensitization and the subsequent  
467 development of allergic diseases.<sup>21,53-58</sup> The presence of allergic march, a process in  
468 which an allergic disease that starts as atopic dermatitis during infancy later develops  
469 into food allergies, bronchial asthma, allergic rhinitis, or conjunctivitis over time during  
470 childhood suggests the importance of promoting research focusing on the successive

471 characteristics of allergic and immunological diseases, including mother-child

472 associations.

473 Action III-1 will cooperate with Actions I-3 and III-2, to drive comprehensive

474 analysis of genetic and environmental factors related to the onset of allergic and

475 immunological diseases using data and samples from preexisting cohort studies,

476 including information from mothers as much as possible. Studies on disease

477 pathophysiology using appropriate model organisms will also be promoted. Advanced

478 Research & Development Programs for Medical Innovation (AMED-CREST, PRIME)

479 have promoted cutting-edge R&D in the specific area designated by MEXT. The

480 program launched the novel area in 2019, to develop a comprehensive understanding of

481 various biological phenomena at the early stage of life,<sup>59</sup> where innovative synergy is

482 expected with *Strategy 2030*. By identifying high-risk group(s) of patients and/or their

483 families extracted from the analysis as well as the preventive measures for that group,

484 scientific information will be provided to potentially reduce the prevalence of allergic

485 and immunological diseases.

486

487 III-2. Research on adult-onset allergic and immunological disease including elderly

488 patients

489 Some allergic and immunological diseases, including bronchial asthma, rhinitis,  
490 sinusitis, contact dermatitis, and drug hypersensitivity often show adult-onset symptoms  
491 that are also found in the elderly.<sup>60,61</sup> The adult-onset group of atopic dermatitis patients  
492 also has different characteristics.<sup>62</sup> In contrast to childhood atopic-type allergies, in  
493 which type-2 cytokines and IgE are the primary actors, adult-onset allergies have  
494 complicated disease states with multiple causative factors, such as age-related changes  
495 in skin and mucosal barrier functions or immunosenescence. Allergic diseases are often  
496 more severe or fatal in adults compared to children and have characteristics such as  
497 exacerbation despite responsiveness to systemic steroid administration. An example of  
498 this is allergy-related severe respiratory disorder, which develops from  
499 aspirin-exacerbated respiratory disease (AERD) or allergic bronchopulmonary mycosis  
500 (ABPM). Thus, measures aimed at combating these diseases are required urgently.

501 Studies on aging are being conducted actively worldwide. AMED-CREST has  
502 launched its novel research area to clarify the mechanisms underlying functional  
503 impairment among individuals over their lifetime.<sup>63</sup> The Nature Partner Journals *Aging*



504 *and Mechanisms of Disease* has also been launched recently.<sup>64</sup> On the other hand, a  
505 comprehensive analysis of adult-onset allergies is not sufficient both domestically and  
506 internationally. Thus, Action III-2 will collaborate with Actions III-1 and III-3 to  
507 promote comprehensive and cross-sectional studies on the natural course of adult-onset  
508 allergic and immunological diseases. Clustering of adult-onset allergies will be  
509 attempted. Collaboration will be initiated with basic researchers, including *in vivo*  
510 analysis using animal models, and the analysis of the mechanisms underlying  
511 age-related changes or immunosenescence.

512 A recent Japanese study conducted among supercentenarians, rare individuals who  
513 live for more than 110 years, have revealed that they have unique immunological  
514 characteristics in their circulating lymphocytes via single-cell transcriptome analysis.<sup>65</sup>  
515 Such unique studies conducted in Japan, a society aging at a globally unprecedented  
516 pace, may allow us to eventually lead other countries in this research field.

517

518 **III-3. Research on severe, intractable, and treatment-resistant allergic and**  
519 **immunological diseases**

520 Approximately 50–70 fatalities occur due to anaphylaxis per year in Japan. The most  
521 common causative allergens reported are pharmaceutical drugs. The fatality rate of  
522 toxic epidermal necrolysis, which is known to be one of the most severe drug allergies,  
523 is reported to be between 20 and 40 percent.<sup>66</sup> Drug-induced hypersensitivity syndrome  
524 (DiHS) is a type of severe drug eruption, and its concept as a disease originated from  
525 Japan. Recent accumulating studies have revealed some cases of death due to  
526 complications of autoimmune diseases during the course of DiHS.<sup>66</sup> Despite the  
527 widespread use of epinephrine autoinjectors in recent years, fatalities resulting from  
528 anaphylaxis induced by food allergens have not been eliminated.

529       Herein, Action III-3, in cooperation with Action III-2 and III-4, will promote  
530 research to elucidate the long-term pathophysiology of severe, intractable, and  
531 treatment-resistant allergic and immunological diseases and the effects of each life stage.  
532 Specifically, the details of preventable symptoms, complications, and/or relapse will be  
533 investigated from studies on natural history. It is also important to clarify the safety,  
534 efficacy, and cost of novel treatments such as allergen immunotherapy and biologics.  
535 The systematic dissemination of evidence necessary for proper use of these treatments  
536 is expected to contribute to the societal implementation of standard treatment for severe

537 and intractable allergic and immunological diseases from childhood to adulthood, and to  
538 zero the number of “preventable deaths” (deaths among patients due to lack of proper  
539 medical management).

540

541 **III-4. Research on allergy and immunology related to rare diseases**

542 Analysis of the pathophysiology underlying rare genetic disorders is an important R&D  
543 strategy in searching for innovative R&D seeds for common diseases, including allergic  
544 and immunological diseases. Given the success of the transformation of R&D from the  
545 rare diseases area to common diseases, such as, the anti-RANKL monoclonal antibody  
546 (from osteopetrosis to osteoporosis), PCSK9 inhibitor (from familial  
547 hypercholesterolemia to hyperlipidemia), and SGLT2 inhibitor (from familial renal  
548 glucosuria to diabetes), not only startup companies but also many large pharmaceutical  
549 companies have taken on their efforts on this scheme. R&D on rare diseases is also  
550 promoted by the Food and Drug Administration (FDA),<sup>67</sup> European Medicines Agency  
551 (EMA),<sup>68</sup> and the MHLW and Pharmaceuticals and Medical Devices Agency (PMDA)  
552 in Japan.<sup>69,70</sup>

553 Other pioneering strategies in this realm are the Initiative on Rare and Undiagnosed  
554 Diseases (IRUD)<sup>15,16</sup> and the Rare Disease Data Registry of Japan (RADDAR-J).<sup>71</sup>  
555 Patient data registration in the Human Phenotype Ontology format has been  
556 standardized<sup>14</sup> and has already contributed greatly to diagnosis, treatment, and medical  
557 care, in combination with the maximum output from next generation sequencing.  
558 Dozens of new diseases have been already identified for the first time globally. To link  
559 the questions of IRUD clinicians to basic research, a “reverse translational research”  
560 platform (the Japanese Rare Disease Models and Mechanisms Network (J-RDMM)) has  
561 been developed on functional analysis of genetic variants.<sup>72</sup> The network is developing  
562 the international consortium for utilizing related model organisms.<sup>73</sup>

563 Action III-4 will promote collaboration with and effective utilization of these rare  
564 disease strategies, aiming to increase the number of R&D seeds and to identify novel  
565 therapies from developmental paths that are different from those in the past. These  
566 collaborations are expected to contribute not only to bilateral R&D promotion between  
567 the allergic and immunological realm and rare disease, but also to other disease realms  
568 as an important role model.

569

570 **Future perspectives**

571 Basic immunological research conducted in Japan has made great discoveries, such as  
572 those regarding IgE and its allergic pathogenesis,<sup>74</sup> immunoglobulin gene  
573 rearrangement,<sup>75</sup> and the immune checkpoint system.<sup>76</sup> To build on and advance these  
574 historical achievements further, this paper, titled *Strategic Outlook toward 2030:*  
575 *Japan's Research for Allergy and Immunology*, was formulated to focus on diversity  
576 and interdisciplinarity, in hopes that it will be of interest not only to researchers but a  
577 broader readership in Japan and beyond, strengthening international cooperation. To  
578 achieve our goals, it is essential to make effective use of our limited research resources  
579 (human, financial, and time), drawing on the efforts of all stakeholders and the unique  
580 R&D ecosystem in Japan, and cooperating with relevant societies, including the  
581 Japanese Society of Allergy. In the next 10 years, it is also indispensable to understand  
582 the grand design of global research for allergy and immunology and the evolution of  
583 patient and public needs, which will be re-evaluated in the mid-term review. Needless to  
584 say, re-investigation of the state of the art in immunology and allergy and re-adjustment  
585 of the strategy are necessary for a sustainable platform.

586           Research in the fields of allergy and immunology aims at contributing toward a  
587   stable society in which people can live long, healthy lives at each life stage. We believe  
588   that in fulfilling our ambitious vision, goals, and actions over the next 10 years, not only  
589   will Japan become a world leader in the life sciences and technology, but will contribute  
590   toward the wellbeing of patients suffering from allergic and immunological diseases and  
591   their families, and advance knowledge in other areas of disease for the benefit of the  
592   nation as a whole.

593

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603

604 **References**

605 1. New Year's Greetings from Toyota President Watanabe. Available at:

606 <https://global.toyota/en/detail/268589> or <https://global.toyota/jp/detail/1268182>

607 [Accessed January 12, 2020] (in Japanese).

608 2. Ministry of Health, Labour, and Welfare, Japan. [Current status of measures against

609 rare/intractable diseases and children's chronic specific diseases]. Available at:

610 <https://www.mhlw.go.jp/content/10601000/000510139.pdf> [Accessed January 12,

611 2020] (in Japanese).

612 3. Ministry of Health, Labour, and Welfare, Japan. [The Basic Law on Measures

613 Against Allergic Diseases]. Available at:

614 [https://www.mhlw.go.jp/web/t\\_doc?dataId=78ab4117&dataType=0&pageNo=1](https://www.mhlw.go.jp/web/t_doc?dataId=78ab4117&dataType=0&pageNo=1)

615 [Accessed January 12, 2020] (in Japanese).

616 4. Ministry of Health, Labour, and Welfare, Japan. [The Basic Guideline for

617 Promoting Measures Against Allergic Diseases]. Available at:

- 618 [https://www.mhlw.go.jp/web/t\\_doc?dataId=00010380&dataType=0&pageNo=1](https://www.mhlw.go.jp/web/t_doc?dataId=00010380&dataType=0&pageNo=1)  
619 [Accessed January 12, 2020] (in Japanese).
- 620 5. Ministry of Health, Labour, and Welfare, Japan. [A Report from Study Committee  
621 on Rheumatoid Arthritis and Allergy]. Available at:  
622 <https://www.mhlw.go.jp/stf/shingi/2r9852000001nes4-att/2r9852000001newa.pdf>  
623 [Accessed January 12, 2020] (in Japanese).
- 624 6. Noda S, Suárez-Fariñas M, Ungar B, Kim SJ, de Guzman Strong C, Xu H, et al.  
625 The Asian atopic dermatitis phenotype combines features of atopic dermatitis and  
626 psoriasis with increased TH17 polarization. *J Allergy Clin Immunol* 2015; **136**:  
627 1254-64.
- 628 7. Adachi T, Kainuma K, Asano K, Amagai M, Arai H, Ishii KJ, et al. [Strategic  
629 Outlook toward 2030: Japan's Research for Allergy and Immunology]. *Arerugi*  
630 2020; **69**: 23-33 (in Japanese).
- 631 8. Ministry of Health, Labour, and Welfare, Japan. [About Strategic Outlook toward  
632 2030: Japan's Research for Allergy and Immunology]. Available at:  
633 <https://www.mhlw.go.jp/content/10901000/000472536.pdf> [Accessed January 12,  
634 2020] (in Japanese).



- 635 9. Robinson PN. Deep phenotyping for precision medicine. *Hum Mutat* 2012; **33**:  
636 777-80.
- 637 10. Agache I, Akdis C, Jutel M, Virchow JC. Untangling asthma phenotypes and  
638 endotypes. *Allergy* 2012; **67**: 835-46
- 639 11. Galli SJ. Toward precision medicine and health: Opportunities and challenges in  
640 allergic diseases. *J Allergy Clin Immunol* 2016; **137**: 1289-300.
- 641 12. The Japan Environment and Children's Study. Available at:  
642 <https://www.env.go.jp/chemi/ceh/en/index.html> [Accessed January 12, 2020].
- 643 13. Kuriyama S, Yaegashi N, Nagami F, Arai T, Kawaguchi Y, Osumi N, et al. The  
644 Tohoku Medical Megabank Project: design and mission. *J Epidemiol* 2016; **26**:  
645 493-511.
- 646 14. Köhler S, Doelken SC, Mungall CJ, Bauer S, Firth HV, Bailleul-Forestier I, et al.  
647 The Human Phenotype Ontology project: linking molecular biology and disease  
648 through phenotype data. *Nucleic Acids Res* 2014; **42**: 966-74.
- 649 15. Adachi T, Kawamura K, Furusawa Y, Nishizaki Y, Imanishi N, Umehara S, et al.  
650 Japan's initiative on rare and undiagnosed diseases (IRUD): towards an end to the  
651 diagnostic odyssey. *Eur J Human Genet* 2017; **25**: 1025-8.

- 652 16. Adachi T, Imanishi N, Ogawa Y, Furusawa Y, Izumida Y, Izumi Y, et al. Survey  
653 on patients with undiagnosed diseases in Japan: potential patient numbers  
654 benefiting from Japan's initiative on rare and undiagnosed diseases (IRUD).  
655 *Orphanet J Rare Dis* 2018; **13**: 208.
- 656 17. De Jager PL, Hacohen N, Mathis D, Regev A, Stranger BE, Benoist C. ImmVar  
657 project: Insights and design considerations for future studies of "healthy" immune  
658 variation. *Semin Immunol* 2015; **27**: 51-7.
- 659 18. Teruel M, Chamberlain C, Alarcón-Riquelme ME. Omics studies: their use in  
660 diagnosis and reclassification of SLE and other systemic autoimmune diseases.  
661 *Rheumatology (Oxford)* 2017; **56**: i78-87.
- 662 19. The Big Data to Knowledge (BD2K) program. Available at:  
663 <https://commonfund.nih.gov/bd2k> [Accessed January 12, 2020].
- 664 20. Electronic Medical Records and Genomics (eMERGE) Network. Available at:  
665 [https://www.genome.gov/27540473/electronic-medical-records-and-genomics-emer](https://www.genome.gov/27540473/electronic-medical-records-and-genomics-emerge-network/)  
666 [ge-network/](https://www.genome.gov/27540473/electronic-medical-records-and-genomics-emerge-network/) [Accessed January 12, 2020].
- 667 21. Natsume O, Kabashima S, Nakazato J, Yamamoto-Hanada K, Narita M, Kondo M,  
668 et al. PETIT Study Team. Two-step egg introduction for prevention of egg allergy

669 in high-risk infants with eczema (PETIT): a randomised, double-blind,  
670 placebo-controlled trial. *Lancet* 2017; **389**: 276-86.

671 22. Kobayashi T, Glatz M, Horiuchi K, Kawasaki H, Akiyama H, Kaplan DH, et al.  
672 Dysbiosis and Staphylococcus Aureus Colonization Drives Inflammation in Atopic  
673 Dermatitis. *Immunity* 2015; **42**: 756-66.

674 23. Morita H, Tamari M, Fujiwara M, Motomura K, Koezuka Y, Ichien G, et al.  
675 IgE-class-specific immunosuppression in offspring by administration of anti-IgE to  
676 pregnant mice. *J Allergy Clin Immunol* 2019; **143**: 1261-4.

677 24. Muraro A, Lemanske RF Jr, Castells M, Torres MJ, Khan D, Simon HU, et al.  
678 Precision medicine in allergic disease-food allergy, drug allergy, and  
679 anaphylaxis-PRACTALL document of the European Academy of Allergy and  
680 Clinical Immunology and the American Academy of Allergy, Asthma and  
681 Immunology. *Allergy* 2017; **72**:1006-21.

682 25. Orellano P, Quaranta N, Reynoso J, Balbi B, Vasquez J. Effect of outdoor air  
683 pollution on asthma exacerbations in children and adults: Systematic review and  
684 multilevel meta-analysis. *PLoS One* 2017; **12**: e0174050.

- 685 26. Hizawa N. Clinical approaches towards asthma and chronic obstructive pulmonary  
686 disease based on the heterogeneity of disease pathogenesis. *Clin Exp Allergy* 2016;  
687 46: 678-87.
- 688 27. Stein MM, Hrusch CL, Gozdz J, Igartua C, Pivniouk V, Murray SE, et al. Innate  
689 immunity and asthma risk in Amish and Hutterite farm children. *N Engl J Med*  
690 2016; **375**: 411-21.
- 691 28. Tanaka J, Fukutomi Y, Kitahara A, Onita K, Okada N, Hattori S, et al.  
692 [Examination of allergen-specific IgE antibody possession status in Japanese adults  
693 using Japanese Red Cross Storage samples]. *Arerugi* 2019; **68**: 499 (in Japanese).
- 694 29. Yamada T, Saito H, Fujieda S. Present state of Japanese cedar pollinosis:  
695 the national affliction. *J Allergy Clin Immunol* 2014; **133**: 632-9.e5.
- 696 30. Pongcharoen P, Fleischer AB Jr. An evidence-based review of systemic treatments  
697 for itch. *Eur J Pain* 2016; **20**: 24-31.
- 698 31. Jensen-Jarolim E, Pali-Schöll I, Roth-Walter F. Outstanding animal studies in  
699 allergy II. From atopic barrier and microbiome to allergen-specific immunotherapy.  
700 *Curr Opin Allergy Clin Immunol* 2017; **17**: 180-7.

- 701 32. Bunyavanich S, Schadt EE. Systems biology of asthma and allergic diseases: a  
702 multiscale approach. *J Allergy Clin Immunol* 2015; **135**: 31-42.
- 703 33. Murayama Y, Shioya H, Tadaki H, Miyamoto M, Yoshihara S, Tabata H, et al.  
704 Objective evaluation of wheezing in normal infants. *Pediatr Int* 2019; **61**: 956-61.
- 705 34. Patient and Public Involvement Policy. Available at:  
706 <https://www.nice.org.uk/about/nice-communities/public-involvement/patient-and-p>  
707 [ublic-involvement-policy](https://www.nice.org.uk/about/nice-communities/public-involvement/patient-and-p) [Accessed January 12, 2020].
- 708 35. PPI Guide Book. Available at: <https://www.amed.go.jp/ppi/guidebook.html>  
709 [Accessed January 12, 2020].
- 710 36. International Rare Diseases Research Consortium. Patient Advocates Constituent  
711 Committee (PPAC). Available at:  
712 <http://www.irdirc.org/about-us/people-organisation/constituent-committees/pacc/>  
713 [Accessed January 12, 2020].
- 714 37. NPO Japan Allergy Tomono Kai. Available at: <http://www.allergy.gr.jp/activity/>  
715 [Accessed January 12, 2020].

- 716 38. Bousquet J, Schunemann HJ, Fonseca J, Samolinski B, Bachert C, Canonica GW,  
717 et al. MACVIA-ARIA Sentinel Network for allergic rhinitis (MASK-rhinitis): the  
718 new generation guideline implementation. *Allergy* 2015; **70**: 1372-92.
- 719 39. Yang HJ, Kim YH, Lee B, Kong DY, Kim DK, Kim MA, et al. Unmet primary  
720 physicians' needs for allergic rhinitis care in Korea. *Allergy Asthma Immunol Res*  
721 2017; **9**: 265-71.
- 722 40. Reyes NJ, O'Koren EG, Saban DR. New insights into mononuclear phagocyte  
723 biology from the visual system. *Nat Rev Immunol* 2017; **17**: 322-32.
- 724 41. Stefania D, Vergara D. The many-faced program of epithelial-mesenchymal  
725 transition: a system biology-based view. *Front Oncol* 2017; **7**: 274.
- 726 42. Tsigkinopoulou A, Baker SM, Breitling R. Respectful modeling: addressing  
727 uncertainty in dynamic system models for molecular biology. *Trends Biotechnol*  
728 2017; **35**: 518-29.
- 729 43. Bunyavanich S, Schadt EE. Systems biology of asthma and allergic diseases: a  
730 multiscale approach. *J Allergy Clin Immunol* 2015; **135**: 31-42
- 731 44. The U.S. Department of Health and Human Services. Revised Common Rule.  
732 Available at:

733 [https://www.hhs.gov/ohrp/regulations-and-policy/regulations/finalized-revisions-co](https://www.hhs.gov/ohrp/regulations-and-policy/regulations/finalized-revisions-common-rule/index.html)  
734 [mmon-rule/index.html](https://www.hhs.gov/ohrp/regulations-and-policy/regulations/finalized-revisions-common-rule/index.html) [Accessed March 5, 2020].

735 45. The European Parliament and of the Council. Regulation (EU) No 536/2014.

736 Available at:

737 [https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg\\_2014\\_536/reg](https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf)  
738 [\\_2014\\_536\\_en.pdf](https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf) [Accessed March 5, 2020].

739 46. Ministry of Health, Labour and Welfare, Japan. Ethical Guidelines for Medical and

740 Health Research Involving Human Subjects. Available at:

741 [https://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikaga](https://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000080278.pdf)  
742 [kuka/0000080278.pdf](https://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000080278.pdf) [Accessed January 12, 2020].

743 47. Ministry of Education, Culture, Sports, Science and Technology, Japan; Ministry of

744 Health, Labour and Welfare, Japan; Ministry of Economy, Trade and Industry,

745 Japan. Ethical Guidelines for Human Genome/Gene Analysis Research. Available

746 at: [https://www.lifescience.mext.go.jp/files/pdf/n796\\_00.pdf](https://www.lifescience.mext.go.jp/files/pdf/n796_00.pdf) [Accessed January 12,  
747 2020).

748 48. Ministry of Health, Labour and Welfare, Japan. [The Clinical Research Core

749 Hospitals]. Available at:

750 <https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/tyukaku.html> [Accessed January  
751 12, 2020] (in Japanese).

752 49. Ministry of Health, Labour and Welfare study group. [A report on the allergic  
753 disease medical provision system]. Available at:  
754 <https://www.mhlw.go.jp/file/05-Shingikai-10901000-Kenkoukyoku-Soumuka/0000>  
755 [172967.pdf](https://www.mhlw.go.jp/file/05-Shingikai-10901000-Kenkoukyoku-Soumuka/0000172967.pdf) [Accessed January 12, 2020] (in Japanese).

756 50. Ministry of Education, Culture, Sports, Science and Technology, Japan. Reform of  
757 Higher Education and Research (Shibayama Initiative). Available at:  
758 [https://www.mext.go.jp/component/a\\_menu/other/detail/\\_\\_icsFiles/afieldfile/2019/](https://www.mext.go.jp/component/a_menu/other/detail/__icsFiles/afieldfile/2019/08/20/1413322_03.pdf)  
759 [08/20/1413322\\_03.pdf](https://www.mext.go.jp/component/a_menu/other/detail/__icsFiles/afieldfile/2019/08/20/1413322_03.pdf) [Accessed January 12, 2020].

760 51. Human Frontier Science Program. Available at: <http://www.hfsp.org> [Accessed  
761 January 12, 2020].

762 52. The Interstellar Initiative. Available at:  
763 [https://www.nyas.org/landing/the-interstellar-initiative-aligning-young-stars-of-scie](https://www.nyas.org/landing/the-interstellar-initiative-aligning-young-stars-of-science-to-tackle-the-world-s-most-critical-medical-challenges/)  
764 [nce-to-tackle-the-world-s-most-critical-medical-challenges/](https://www.nyas.org/landing/the-interstellar-initiative-aligning-young-stars-of-science-to-tackle-the-world-s-most-critical-medical-challenges/) [Accessed January 12,  
765 2020].



- 766 53. Horimukai K, Morita K, Narita M, Kondo M, Kitazawa H, Nozaki M, et al.  
767 Application of moisturizer to neonates prevents development of atopic dermatitis. *J*  
768 *Allergy Clin Immunol* 2014; **134**: 824-30.
- 769 54. Simpson EL, Chalmers JR, Hanifin JM, Thomas KS, Cork MJ, McLean WH, et al.  
770 Emollient enhancement of the skin barrier from birth offers effective atopic  
771 dermatitis prevention. *J Allergy Clin Immunol* 2014; **134**: 818-23.
- 772 55. Fernández-Rivas M, Barreales L, Mackie AR, Fritsche P, Vázquez-Cortés S,  
773 Jedrzejczak-Czechowicz M, et al. The EuroPrevall outpatient clinic study on food  
774 allergy: background and methodology. *Allergy* 2015; **70**: 576-84.
- 775 56. Gough H, Grabenhenrich L, Reich A, Eckers N, Nitsche O, Schramm D, et al.  
776 Allergic multimorbidity of asthma, rhinitis and eczema over 20 years in the German  
777 birth cohort MAS. *Pediatr Allergy Immunol* 2015; **26**:431-7.
- 778 57. McGowan EC, Bloomberg GR, Gergen PJ, Visness CM, Jaffee KF, Sandel M, et al.  
779 Influence of early-life exposures on food sensitization and food allergy in an  
780 inner-city birth cohort. *J Allergy Clin Immunol* 2015; **135**: 171-8.

- 781 58. Bisgaard H, Vissing NH, Carson CG, Bischoff AL, Følsgaard NV, Kreiner-Møller  
782 E, et al. Deep phenotyping of the unselected COPSAC2010 birth cohort study. *Clin*  
783 *Exp Allergy* 2013; **43**: 1384-94.
- 784 59. AMED-CREST, PRIME. Understanding of the biological phenomena and  
785 responses at the early life stages to improve the quality of health and medical care.  
786 Available at [https://www.amed.go.jp/en/program/list/04/02/001\\_13.html](https://www.amed.go.jp/en/program/list/04/02/001_13.html) [Accessed  
787 January 12, 2020].
- 788 60. Dunn RM, Busse PJ, Wechsler ME. Asthma in the elderly and late-onset adult  
789 asthma. *Allergy* 2018; **73**: 284-94.
- 790 61. Matsusaka M, Kabata H, Fukunaga K, Suzuki Y, Masaki K, Mochimaru T, et al.  
791 Phenotype of asthma related with high serum periostin levels. *Allergol Int* 2015; **64**:  
792 175-80.
- 793 62. Tanei R, Hasegawa Y. Atopic dermatitis in older adults: A viewpoint from geriatric  
794 dermatology. *Geriatr Gerontol Int* 2016; **16**: 75-86.
- 795 63. AMED-CREST, PRIME. Clarification of the mechanism of individual's functional  
796 impairment over the entire life course. Available at:

797 [https://www.amed.go.jp/en/program/list/04/02/001\\_11.html](https://www.amed.go.jp/en/program/list/04/02/001_11.html) [Accessed January 12,  
798 2020].

799 64. Nature Partner Journals. Aging and Mechanisms of Disease. Available at:  
800 <https://www.nature.com/npjamd/> [Accessed January 12, 2020].

801 65. Hashimoto K, Kouno T, Ikawa T, Hayatsu N, Miyajima Y, Yabukami H, et al.  
802 Single-cell transcriptomics reveals expansion of cytotoxic CD4 T cells in  
803 supercentenarians. *Proc Natl Acad Sci* 2019; **116**: 24242-51.

804 66. Shiohara T, Mizukawa Y. Drug-induced hypersensitivity syndrome (DiHS)/drug  
805 reaction with eosinophilia and systemic symptoms (DRESS): An update in 2019.  
806 *Allergol Int* 2019; **68**: 301-8.

807 67. United States Food and Drug Administration. Developing Products for Rare  
808 Diseases & Conditions. Available at:  
809 <https://www.fda.gov/industry/developing-products-rare-diseases-conditions>  
810 [Accessed January 12, 2020].

811 68. European Medicines Agency. PRIME – Priority Medicines. Available at:  
812 [https://www.ema.europa.eu/en/documents/leaflet/prime-paving-way-promising-me  
813 dicines-patients-factsheet\\_en.pdf](https://www.ema.europa.eu/en/documents/leaflet/prime-paving-way-promising-medicines-patients-factsheet_en.pdf) [Accessed January 12, 2020].

- 814 69. Ministry of Health, Labour and Welfare. [Implementation of the Conditional Early  
815 Approval System for Pharmaceuticals]. Available at  
816 <https://www.pmda.go.jp/files/000220723.pdf> [Accessed January 12, 2020] (in  
817 Japanese).
- 818 70. Ministry of Health, Labour and Welfare. [Overview of the Designation System for  
819 Orphan Drugs, Orphan Medical Devices, and Orphan Regenerative Medicine  
820 Products]. Available at:  
821 <https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000068484.html> [Accessed  
822 January 12, 2020] (in Japanese).
- 823 71. Furusawa Y, Yamaguchi I, Yagishita N, Tanzawa K, Matsuda F, Yamano Y, et al.  
824 National platform for rare diseases data registry of Japan. *Learn Health Syst* 2019;  
825 **3**: e10080
- 826 72. Japanese Rare Disease Models and Mechanisms Network. Available at:  
827 <https://j-rdmm.org/indexEn.html> [Accessed January 12, 2020].
- 828 73. Oriel C, Lasko P. Recent developments in using drosophila as a model for human  
829 genetic disease. *Int J Mol Sci* 2018; **19**: 2041.

830 74. The Japan Prize Foundation. Laureates of the Japan Prize 2000. Available at:  
831 [https://www.japanprize.jp/en/prize\\_prof\\_2000\\_ishizaka.html](https://www.japanprize.jp/en/prize_prof_2000_ishizaka.html) [Accessed January 12,  
832 2020].

833 75. The Nobel Assembly at the Karolinska Institute. The Nobel Prize in Physiology or  
834 Medicine 1987. Available at:  
835 <https://www.nobelprize.org/prizes/medicine/1987/press-release/> [Accessed January  
836 12, 2020].

837 76. Nobel Media. The Nobel Prize in Physiology or Medicine 2018. Available at:  
838 <https://www.nobelprize.org/prizes/medicine/2018/summary/> [Accessed January 12,  
839 2020].

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841

842 **Figure legends**

843 Figure 1. Developmental process for *Strategic Outlook toward 2030: Japan's Research*  
844 *for Allergy and Immunology*.

845 Figure 2. Vision, goals, and actions of *Strategic Outlook toward 2030: Japan's*  
846 *Research for Allergy and Immunology*.

847 Figure 3. Positioning of *Strategic Outlook toward 2030: Japan's Research for Allergy*  
848 *and Immunology*.

849 Figure 4. Scheme of 12 actions of *Strategic Outlook toward 2030: Japan's Research for*  
850 *Allergy and Immunology*.

851

Figure 1

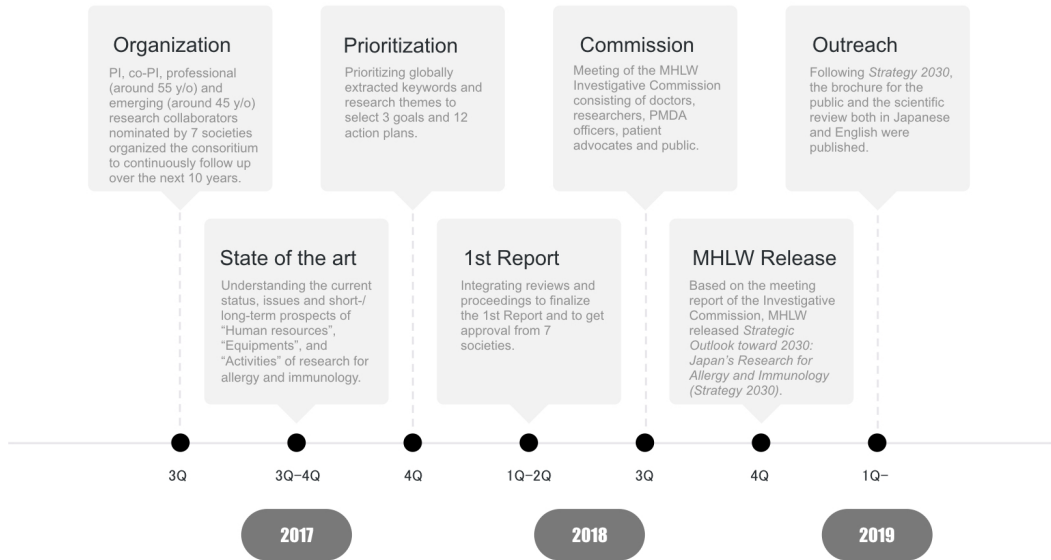


Figure 2

Vision : With patient and public involvement, as well as industry-academia-government collaborations, enable all people live long, healthy lives as free as possible from allergic and immunological diseases, at each individual life stage, through: elucidation of the pathophysiology; identification of the disease activity and unmet needs; implementation of precision medicine with preemptive treatments; and eradication of the preventable deaths

Goal 1 : Elucidate the pathophysiology of allergic and immunological diseases via promoting basic, epidemiological, and clinical research to realize precision medicine with innovative preemptive treatments



Preemptive  
ActionsI: Fundamental research for pathophysiological elucidation and innovative preemptive treatments

Goal 2 : Establish an interdisciplinary system to promote international research and development, aiming to effectively implement it into a society in which patients and the public actively engage



Interdisciplinary  
ActionsII: Cross-sectional research related to effective promotion and societal development

Goal 3 : Spread appropriate prevention and treatment methods widely to society, to optimize medical care according to disease characteristics such as life stages and to eliminate preventable deaths



Life stage  
ActionsIII: Key research focusing on allergic and immunological disease characteristics such as those in different life stages



Figure 3

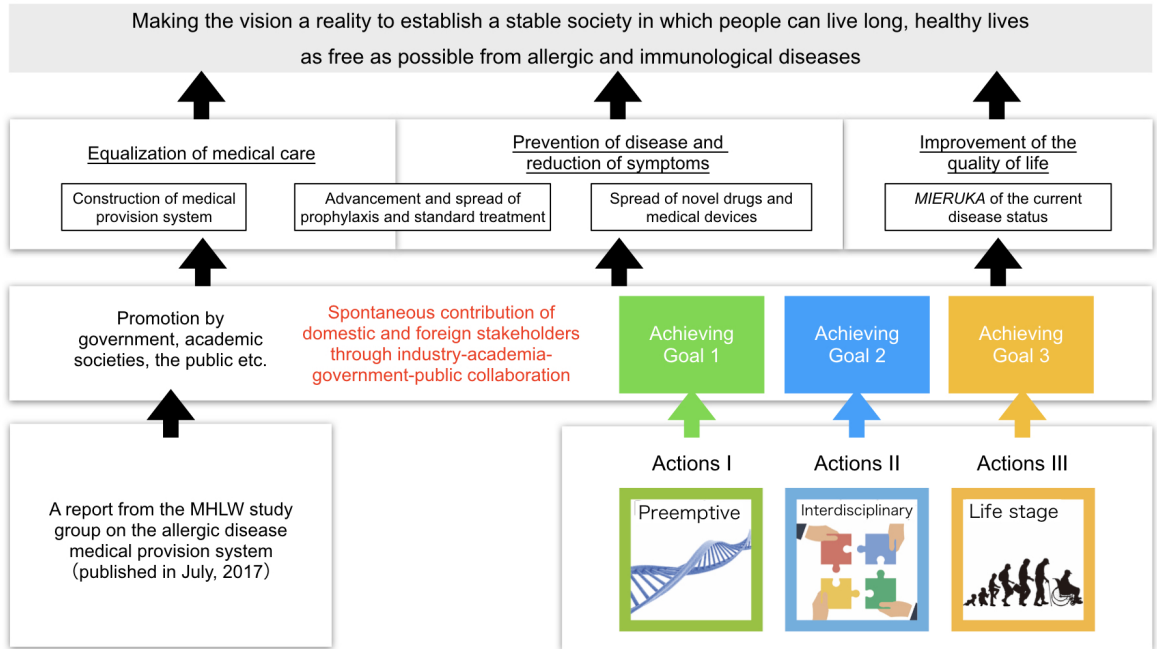


Figure 4

