PERSPECTIVE

Precision management of gene-based tests not covered by the National Health Insurance system in Japan: a questionnaire-based study

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The National Health Insurance (NHI) of Japan is a system whereby all residents of Japan (including citizens and foreigners) must obtain public medical insurance, a requirement intended to reduce the burden of high medical expenses in the event of illness or accident. Since the clinical laboratories that conduct specimen tests covered by medical insurance are clinical laboratories that are registered by each prefecture, such laboratories need to demonstrate high levels of accuracy. However, there are no rules guaranteeing accuracy in facilities and laboratories that perform specimen tests not covered by NHI [1]. Clinical tests that analyze genes relevant to medical treatment are collectively called gene-based tests, and they are classified into three types: pathogen genetic testing (nucleic acid testing), human somatic genetic testing, and human germline genetic testing [2]. Gene-based tests have been reclassified as specimen tests by the Clinical Laboratory Law Enforcement Regulations enforced in December 2018, stipulating the use of quasi-work-procedure manuals and ledgers, record-of-work diaries, the implementation of internal quality control procedures, external quality assessment survey inspection, and appropriate training of personnel for precision management [3]. At the present time, Japan has listed 20 items under pathogen genetic testing, 19 under somatic genetic testing, and 140 syndromes (diseases) under germline genetic testing covered by the NHI system; however, the many remaining items are not covered by the NHI system [4]. Pathogen genetic testing accounts for the majority of the total number of gene-based tests. Additionally, despite the importance of such tests for the diagnosis and treatment of infectious diseases, new tests have to be implemented in facilities and laboratories every time a new infectious disease emerges (e.g., COVID-19); this process creates challenges in terms of quality control. The nature of gene-based tests in Japan requires an assessment of the precision management of tests not covered by the NHI. As mentioned above, gene-based tests not covered by insurance occupy an important position in Japan, but, unfortunately, the actual status of the guarantee of their accuracy is not understood, and many of them are not appropriately managed.

The aim of this study was to conduct a questionnaire-based study of facilities and laboratories in Japan and to assess the quality management of gene-based tests not covered by NHI.

From December 2019 to February 2020, questionnaires were sent by e-mail or post to a total of 332 facilities and laboratories classified into three categories: members of the Japan Registered Clinical Laboratories Association; members of the National Liaison Council for Clinical Sections of Medical Genetics; and individual laboratories at universities. Since it was not known which facilities and laboratories participated in the practice of gene-based tests, all were identified based on their registration information and targeted without setting any selection criteria. For facilities and laboratories responding to the questionnaire electronically, a special website that permitted the respondents to answer questions by selecting (clicking) from among the items was created. In addition, respondents were permitted to enter free text when detailed information was required. The completed questionnaires were returned via the website, facsimile, or post.

This study was designed to serve as an international standard for the quality and accuracy of tests related to biobanks and genomic medicine and supported by the Japan Agency for Medical Research and Development (AMED) [5], and carried out as research (conducted by Research and Development Representative Tohru Masui) on the construction and implementation of a biobank collaboration system and genetic-based testing.

Before preparing the questionnaires, several representative laboratories that perform genetic-based testing were interviewed. The sub-items regarding gene-based tests on the questionnaire were composed of questions on basic information for facilities and laboratories (Fig. 1) and 30 items consisting of 10 questions each for the three types of gene-based tests (management in Table 1 and quality control in Table 2). The survey asked for the names of the respondent and the facility/laboratory to which the respondent belonged. The study questionnaire described here was developed by Tomohiro Nakayama following discussions with the AMED Study Group.

All answers were classified by ten specific questions and each of the nine classified groups of the facilities and laboratories. Group comparisons were analyzed using χ^2 tests with Bonferroni correction. *P* values were evaluated using Fisher's exact test. A *P* value <0.05 was considered significant. Data analysis was performed using SPSS statistics ver. 22 (IBM Corporation, Armonk, NY, USA).

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		Clinical laboratory area				Genetic medicine area				Research area			
		No. of gene-based tests (total)	No. of pathogen genetic tests	No. of somatic genetic tests	No. of germline genetic tests	No. of gene-based tests (total)	No. of pathogen genetic tests	No. of somatic genetic tests	No. of germline genetic tests	No. of gene-based tests (total)	No. of pathogen genetic tests	No. of somatic genetic tests	No. of germline genetic tests
Hospitals	Clinical laboratories (divisions)					Genetic medicine (divisions)							
	University	a Clinical laboratories (divisions) of university hospitals				c Departments of genetic medicine (divisions) of university hospitals				g University medical offices/laboratories			
		14	6	5	5	12	1	1	4	55	9	18	32
		b Clinical laboratories (divisions) of hospitals other than those belonging to a university				d Genetic medicine laboratories (divisions) of hospitals other than those belonging to a university				h Laboratories other than university medical divisions/laboratories			
		7	2	3	3	5	1	1	3	6	0	0	3
		e Registered clinical laboratories											
		f Clinical laboratories that are not registered clinical laboratories											
		49	13	4	6								
		i Other											
		1	0	0	0								
		2	0	0	1								

Fig. 1 Classification of facilities and laboratories

From among 332 facilities and laboratories, 151 responded to the questionnaire, for a recovery rate of 45.5%. The operating modes of the 151 responding facilities and laboratories were as follows: (a) 14 were clinical laboratories (divisions) of university hospitals; (b) 7 were clinical laboratories (divisions) of hospitals other than those belonging to universities; (c) 12 were departments of genetic medicine (divisions) of university hospitals; (d) 5 were genetic medicine laboratories (divisions) of hospitals other than those belonging to universities; (e) 49 were registered clinical laboratories; (f) 1 was a clinical laboratory (not a registered clinical laboratory); (g) 55 were university medical divisions/laboratories; (h) 6 were laboratories other than university medical divisions/laboratories; (i) and 2 were “other” (1 pathological diagnosis department at a university hospital and 1 unknown). Figure 1 shows the classifications of the participating facilities and laboratories. All facilities and laboratories were classified into either a clinical laboratory area, a genetic medicine area, or a research area; the numbers of gene-based tests consisting of pathogen genetic testing, somatic genetic testing, and genetic testing performed at each facility are shown in Fig. 1.

Questions and answers regarding facilities and laboratories (Questions 1–4) in terms of the management of the three types of gene-based tests not covered by NHI are shown in Table 1. Among the three types of gene-based tests, the highest percentage requested from outside was for germline genetic testing (74%) not covered by NHI. Basic research equipment, commercial kits, and self-prepared reagents were used at nearly the same level of frequency in all three types of gene-based tests.

Questions and answers regarding the status of quality control in facilities and laboratories (Questions 5–8) for the management of all three types of gene-based tests not covered by NHI are shown in Table 2. Internal quality control was available for more than 90% of the pathogen genetic tests, compared with about 67% of somatic and germline genetic tests. Simultaneous measurement of both positive and negative controls was used most frequently for internal quality control in all three types of gene-based tests. However, more than two-thirds of all types of tests were not subject to external quality control. The College of American Pathologists survey and cross-checks with other facilities were mainly used for external quality control.

All three types of gene-based tests were mostly paid for as research and medical expenses. Less than half of the facilities and laboratories could prepare the required documents for all three types of gene-based tests (Table 2).

Ten specific questions and answers were analyzed in each of the nine classified groups of facilities and laboratories (<https://www.amed.go.jp/content/000071535.pdf>). Although the facilities and laboratories were classified into nine groups, the top two occupied 68.9%: university medical offices/laboratories (36.4%) and registered clinical laboratories (32.5%). When the remaining seven groups were divided into the three types of gene-based tests and analyzed, the number of individual items was very small. Therefore, the top two frequent answers for the 10 specific

questions were analyzed in the registered clinical laboratories and university medical offices/laboratories (Table 3). The performance of pathogen genetic testing was significantly lower for university medical offices/laboratories. External quality control (evaluation) was not frequently performed for somatic and germline genetic testing. Notably, many gene-base tests were paid for as research or medical expenses.

Few reports have been published on the implementation of gene-based tests not covered by NHI in Japan. Thus, the present study provides extremely valuable data, particularly those obtained by analyzing how quality control is performed for each facility and laboratory in each of the three gene-based tests. In the three types of gene-based tests, the percentage performing tests requested from outside was highest for germline genetic testing not covered by NHI, whereas performing tests requested from outside was infrequent for pathogen and somatic genetic testing. The reason why requests from outside were high for germline genetic testing not covered by NHI is likely because most pathogen and somatic genetic testing is covered by NHI.

Research equipment was most frequently used among the top four groups of facilities and laboratories in Japan. When carrying out gene-based tests covered by NHI, Japanese law requires the use of certified clinical laboratory equipment to receive NHI payments. Given that this survey was concerned with gene-based tests not covered by NHI, the use of any equipment would be permitted. It is not surprising that clinical laboratories at departments of university hospitals use certified clinical laboratory equipment more often than research equipment. However, with regard to testing kits, the percentage of facilities and laboratories that use self-prepared (“home-brew”) reagents was higher in the clinical laboratory departments of university hospitals than in registered clinical laboratories, which may be the result of ongoing cost-reduction efforts. Regarding the accuracy of the present results, responses to Question 4 (“How do you adjust the reagents used for gene-based tests not covered by NHI at your facility/laboratory?”) may have been affected by the potential ambiguity of the definition of a purchased kit. For example, in the case of a test using nucleic acid amplification, some practitioners may use buffers and enzymes obtained from a commercially available kit in combination with self-prepared reagents, including positive or negative controls and primers and probes. In this situation, the respondents may have indicated the use of commercially available kits, despite the incorporation of self-prepared reagents. As a result, the percentage of facilities and laboratories that reported buying basic reagent kits may have been erroneously inflated compared with the percentage that reported using self-prepared reagents.

Recently, Adachi et al. [6] reported the status of germline genetic testing for intractable diseases in Japan. They and other researchers pointed out that numerous medical professionals want germline genetic testing to be covered by NHI [7]. However, the present study focused on gene-based testing, including genetic tests not covered by NHI. Although accurate methods and

Table 1. Questions and responses concerning the management of gene-based tests not covered by National Health Insurance

Question No.	Questions	Classification of gene-based tests	Choices				
			a) Yes	b) No	c) Other, free description	d) No description	e) No description
1.	Does your facility/laboratory carry out gene-based tests not covered by National Health Insurance?						
	In case b), proceed to II. In cases other than b), proceed to 2.						
		1) Pathogen genetic testing	32 (21%)	116 (77%)	3 (2%)	0 (0%)	
		2) Somatic genetic testing	32 (21%)	119 (79%)	0 (0%)	0 (0%)	
		3) Germline genetic testing	57 (38%)	92 (61%)	2 (1%)	0 (0%)	
2.	Does your facility/laboratory accept analysis requests from outside facilities for gene-based tests not covered by National Health Insurance?		a) Yes	b) No	c) Other, free description	d) No description	
		1) Pathogen genetic testing	18 (12%)	31 (21%)	0 (0%)	102 (68%)	
		2) Somatic genetic testing	16 (11%)	21 (14%)	0 (0%)	114 (75%)	
		3) Germline genetic testing	42 (74%)	12 (21%)	3 (5%)	94 (62%)	
3.	Does the equipment used for gene-based tests not covered by insurance at your facility or laboratory consist of basic research equipment or clinical testing equipment?		a) Basic research equipment	b) Certified clinical laboratory equipment	c) Other, free description	d) Both types	e) No description
	* The handling of certified clinical laboratory equipment is regulated by the Pharmaceutical and Medical Device Act (by the Director of Office of Medical Devices Evaluation (OMDE), Evaluation and Licensing Division (ELD), Pharmaceutical Safety and Environmental Health Bureau (PSEHB), Notification No. 0428-1, Compliance and Narcotics Division, Pharmaceutical Safety and Environmental Health Bureau (PSEHB), Notification No. 0428-1) (https://www.pmda.go.jp/files/000213137.pdf).	1) Pathogen genetic testing	23 (72%)	6 (19%)	0 (0%)	3 (9%)	119
		2) Somatic genetic testing	24 (75%)	2 (6%)	2 (6%)	4 (13%)	119
		3) Germline genetic testing	47 (82%)	6 (11%)	2 (4%)	2 (4%)	94
4.	How do you obtain reagents used for gene-based tests not covered by National Health Insurance at your facility or laboratory?		a) Commercial kit	b) Self-prepared	c) Other, free description	d) Both ways	e) No description
		1) Pathogen genetic testing	13 (41%)	11 (34%)	0 (0%)	8 (25%)	119
		2) Somatic genetic testing	14 (44%)	11 (34%)	1 (3%)	6 (19%)	119
		3) Germline genetic testing	24 (42%)	23 (40%)	1 (2%)	9 (16%)	94

*Supplementary explanation about the question

Table 2. Questions and responses regarding quality control of gene-based tests not covered by National Health Insurance

Question No.	Questions	Classification of gene-based tests	Choices						
			a) Yes	b) No	c) Other, free description	d) No description	e) The same sample is measured twice using different methods (e.g., direct sequencing and next-generation sequencing).	f) Statistical examination	g) Other, free description
5.	Do you implement internal quality control for gene-based tests not covered by National Health Insurance at your facility/ laboratory?								
		1) Pathogen genetic testing	29 (91%)	3 (9%)	0 (0%)	119			
		2) Somatic genetic testing	21 (66%)	10 (31%)	1 (3%)	119			
		3) Genetic testing	39 (68%)	17 (30%)	1 (2%)	94			
6.	To those who answered a in 5: Please clarify the practice of internal quality control in your facility or laboratory (multiple answers possible).								
		a) Simultaneous measurement of a negative control							
		b) Simultaneous measurement of a positive control							
		c) Another person measures and compares the same sample.							
		d) The same sample is measured twice with the same instrument.							
		e) The same sample is measured twice using different methods (e.g., direct sequencing and next-generation sequencing).							
		1) Pathogen genetic testing	3	4	22	2	3	5	2
		2) Somatic genetic testing	3	1	14	2	5	4	1
		3) Germline genetic testing	7	2	18	7	8	14	2
7.	Does your facility or laboratory carry out external quality control (evaluation) for gene-based tests not covered by National Health Insurance?								
		a) Yes							
		b) No							
		c) Other, free description							
		1) Pathogen genetic testing	11 (34%)	21 (66%)	0 (0%)	119			
		2) Somatic genetic testing	10 (31%)	22 (69%)	0 (0%)	119			
		3) Germline genetic testing	12 (21%)	44 (77%)	1 (2%)	94			
8.	To those who answered a in 7: Please clarify the actual external quality control (evaluation) at your facility or laboratory (multiple answers possible).								
		a) Subject to quality control of gene-based tests by CAP survey							
		b) Subject to quality control by GenQA gene-based tests							
		c) Has undergone other external quality control (evaluation) (program name)							
		d) Cross-check with other facilities							
		e) Other, free description							

Table 2. continued

Question No.	Questions	Classification of gene-based tests	Choices					
	* The College of American Pathologists (CAP) of the American Pathologists Medical Association is an international group that performs external quality control (evaluations). The CAP survey is the largest in the world and currently covers approximately 22,000 clinical laboratories in 108 countries. In gene-based testing, you can select and apply for individual genetic diseases or genes, and a genomic sample will be mailed to you. The laboratory has to provide/synthesize the primers themselves. After sending the results of the determination of the nucleotide sequence variants by facsimile or e-mail to the CAP, the correct answers and a participation certificate are provided within about 1 month.	1) Pathogen genetic testing	4	0	3	6	1	
	* GenQA is a part of the UK National External Quality Assessment Service (UK NEQAS) Consortium, which conducts international external quality assessments of genomics.							
	2) Somatic genetic testing		4	0	1	2	2	
	3) Germline genetic testing		4	0	1	5	2	
		a) Research expenses, medical expenses, etc.		b) Budget of the entire organization (hospital, university, etc.), including facilities and laboratories	c) Patient/client's own expense	d) Request to requesting facility	e) Both a) and b)	f) Unknown
								h) No description

Table 2. continued

Question No.	Questions	Classification of gene-based tests	Choices					
9.	We would like to ask about the implementation costs for gene-based tests not covered by National Health Insurance at your facility or laboratory.		a) Research expenses, medical expenses, etc.	b) The budget of the entire organization (hospital, university, etc.) including facilities and laboratories	c) Patient/client's own expense	d) Invoice sent to requesting facility	Both a and b	
		1) Pathogen genetic testing	11 (34%)	6 (19%)	9 (28%)	3 (9%)	2 (6%)	1 (3%) 119
		2) Somatic genetic testing	24 (75%)	2 (6%)	2 (6%)	2 (6%)	2 (6%)	0 (0%) 119
		3) Germline genetic testing	41 (72%)	1 (2%)	6 (11%)	2 (4%)	5 (9%)	2 (4%) 94
10.	We would like to ask you about the documents prepared by your facility or laboratory regarding gene-based tests not covered by National Health Insurance at your facility or laboratory.		a) We employ all of the documents from ① to ③.	b) Items ② to ③ are available.	c) For those other than a and b, please indicate the number of prepared documents.	h) No description of the facility with answer yes for question 1	h) No description	
	① Serum separation standard workbook, ② Inspection equipment maintenance management standard work manual, ③ Measurement standard work manual (= standard work procedure manual), ④ Reagent management ledger, ⑤ Statistical quality control ledger (internal quality control), ⑥ External quality control ledger, ⑦ Inspection equipment maintenance management work diary, ⑧ Measurement work diary	1) Pathogen genetic testing	8 (25%)	5 (16%)	18 (56%)	1 (3%)	119	
		2) Somatic genetic testing	8 (25%)	2 (6%)	19 (59%)	3 (9%)	119	
		3) Germline genetic testing	6 (11%)	6 (11%)	39 (68%)	6 (11%)	94	

*Supplementary explanation about the question

Table 3. Top two frequent responses for ten specific questions analyzed for registered clinical laboratories and university medical offices/laboratories

	Pathogen genetic testing				Somatic genetic testing				Germline genetic testing			
	Yes	No	p value		Yes	No	p value		Yes	No	p value	
1. Does your facility/laboratory carry out gene-based tests not covered by National Health Insurance?												
	4	2			4	2			6	0		
Registered clinical laboratories												
	6	26	0.031	*	12	20	0.217		32	0	1.000	
University medical offices/laboratories												
2. Does your facility/laboratory accept analysis requests from outside facilities for gene-based tests not covered by national health insurance?	Yes	No	p value		Yes	No	p value		Yes	No	p value	
	4	0			2	1			5	1		
Registered clinical laboratories												
	3	3	0.200		9	2	1.000		25	6	1.000	
University medical offices/laboratories												
3. Is the equipment used for gene-based tests not covered by insurance at your facility or laboratory basic research equipment or clinical testing equipment?	Basic research equipment	Certified clinical laboratory equipment	p value		Basic research equipment	Certified clinical laboratory equipment	p value		Basic research equipment	Certified clinical laboratory equipment	p value	
	4	1			4	2			6	0		
Registered clinical laboratories												
	5	1	1.000		11	2	0.557		30	2	1.000	
University medical offices/laboratories												

Table 3. continued

		Pathogen genetic testing			Somatic genetic testing			Germline genetic testing			
		Commercial kit	Self-prepared		Commercial kit	Self-prepared		Commercial kit	Self-prepared		
4.	How do you obtain reagents used for gene-based tests not covered by National Health Insurance at your facility or laboratory?	Registered clinical laboratories	4	3	4	3		3	6		
		University medical offices/ laboratories	2	3	0.621	8	5	1.000	19	15	0.281
5.	Do you implement internal quality control for gene-based tests not covered by National Health Insurance at your facility/ laboratory?	Yes	No	No	<i>p</i> value	Yes	No	<i>p</i> value	Yes	No	<i>p</i> value
		Registered clinical laboratories	4	0	4	0	0	6	0		
		University medical offices/ laboratories	5	1	1.000	7	5	0.025	19	12	0.149
6.	To those who answered a in 5: Please clarify the practice of internal quality control in your facility or laboratory (multiple answers possible).	Simultaneous measurement of both a positive control and a negative control	The same sample is measured twice using different methods (e.g., direct sequencing and next-generation sequencing).	Simultaneous measurement of both a positive control and a negative control	The same sample is measured twice using different methods (e.g., direct sequencing and next-generation sequencing).	Simultaneous measurement of both a positive control and a negative control	The same sample is measured twice using different methods (e.g., direct sequencing and next-generation sequencing).	Simultaneous measurement of both a positive control and a negative control	The same sample is measured twice using different methods (e.g., direct sequencing and next-generation sequencing).		
		Registered clinical laboratories	4	1	4	0	0	5	1		
		University medical offices/ laboratories	4	0	1.000	4	1	1.000	9	10	0.180

Table 3. continued

	Pathogen genetic testing				Somatic genetic testing				Germline genetic testing			
	a) Yes	b) No	p value		a) Yes	b) No	p value		a) Yes	b) No	p value	
7. Does your facility or laboratory carry out external quality control (evaluation) for gene-based tests not covered by national health insurance?	2	1			4	0			4	2		
	Registered clinical laboratories											
	0	6	0.083		1	11	0.003	*	2	29	0.003	*
	University medical offices/ laboratories											
8. To those who answered a in 7: Please clarify the actual external quality control (evaluation) at your facility or laboratory (multiple answers possible).	Subject to quality control of gene-based tests by CAP survey	Cross-check with other facilities	p value		Subject to quality control of gene-based tests by CAP survey	Cross-check with other facilities	p value		Subject to quality control of gene-based tests by CAP survey	Cross-check with other facilities	p value	
	1	1			3	1			3	0		
	Registered clinical laboratories											
	0	0	1.000		0	1	0.400		0	2	0.100	
	University medical offices/ laboratories											
9. We would like to ask about the implementation costs for gene-based tests not covered by National Health Insurance at your facility or laboratory.	Research expenses, medical expenses, etc.	Patient/ client's own expense	p value		Research expenses, medical expenses, etc.	Patient/ client's own expense	p value		Research expenses, medical expenses, etc.	Patient/ client's own expense	p value	
	1	1			1	1,000			1	2,000		
	Registered clinical laboratories											
	5	0	0.286		12	0.000	0.143	*	28	1,000	0.018	*
	University medical offices/ laboratories											

Table 3. continued

	Pathogen genetic testing			Somatic genetic testing			Germline genetic testing		
	Items ② to ④ are available	Not all of ② to ④ are available	<i>p</i> value	Items ② to ④ are available	Not all of ② to ④ are available	<i>p</i> value	Items ② to ④ are available	Not all of ② to ④ are available	<i>p</i> value
10. We would like to ask you about the documents prepared by your facility or laboratory regarding gene-based tests not covered by National Health Insurance at your facility or laboratory.									
① Serum separation standard workbook, ② Inspection equipment maintenance management standard work manual, ③ Measurement standard work manual (= standard work procedure manual), ④ Reagent management ledger, ⑤ Statistical quality control ledger (internal quality control), ⑥ External quality control ledger, ⑦ Inspection equipment maintenance management work diary, ⑧ Measurement work diary	Registered clinical laboratories	1	0.190	3	1	0.077	3	3	1.000
	University medical offices/ laboratories	5	0.190	2	9	0.077	2	4	1.000

p values were calculated using Fisher's exact test. **p* < 0.05

techniques are necessary to perform gene-based tests in clinical laboratories [8], documentation of quality control is expected to be required in the future, regardless of whether these tests are covered by NHI (Question 10). Of the eight required documents, those that were not prepared did not differ significantly between facilities; however, the least prepared was the external quality control ledger, followed by the statistical quality control ledger (internal quality control). These results indicate a lack of concern, because preparing a ledger does not require any special effort. The present results imply the need for a precision management system for somatic genetic testing, especially for external quality assessment, in Japan.

In conclusion, the main problem of quality control of gene-related tests that are not covered by insurance in Japan is as follows. Basic research equipment was mostly used for all three types of gene-based tests. Commercial kits and self-prepared reagents were used almost equally often for all three types of gene-based tests. More than two-thirds of tests were not subject to external quality control for all three types of gene-based tests. All three types of gene-based tests were mostly paid for as research expenses and medical expenses.

One limitation of this study was that the responses were left to the conscience of the respondents and thus obtained without directly observing the individual facilities and laboratories. However, it is possible that the majority of the respondents answered questions that could expose their weaknesses honestly. The present results suggest the need to build a system that can respond promptly while maintaining a minimal standard of accuracy, regardless of whether the facilities and laboratories in question are performing somatic genetic testing not covered by NHI. The results of the present study will aid in the formulation of indices for quality control in future gene-based tests.

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AUTHOR CONTRIBUTIONS

TN and TM designed research, TN sent the questionnaire to the facilities and laboratories. TN and TM analyzed the results, and wrote the manuscript. TN led and oversaw the project.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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