Biobanking for glomerular diseases: a study design and protocol for KOrea Renal biobank NEtwoRk System TOward NExt-generation analysis (KORNERSTONE)

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Abstract

Backgrounds: Glomerular diseases, a set of debilitating and complex disease entities, are related to mortality and morbidity. To gain insight into pathophysiology and novel treatment targets of glomerular disease, various types of biospecimens linked to deep clinical phenotyping including clinical information, digital pathology, and well-defined outcomes are required. We provide the rationale and design of the KOrea Renal biobank NEtwoRk System TOward Next-generation analysis (KORNERSTONE).

Methods: The KORNERSTONE, which has been initiated by Korea Centres for Disease Control and Prevention, is designed as a multi-centre, prospective cohort study and biobank for glomerular diseases. Clinical data, questionnaires will be collected at the time of kidney biopsy and subsequently every 1 year after kidney biopsy. All of the clinical data will be extracted from the electrical health record and automatically uploaded to the web-based database. High-quality digital pathologies are obtained and connected in the database. Various types of biospecimens are collected at baseline and during follow-up: serum, urine, buffy coat, stool, glomerular complementary DNA (cDNA), tubulointerstitial cDNA. All data and biospecimens are processed and stored in a standardised manner. The primary outcomes are mortality and end-stage renal disease. The secondary outcomes will be deterioration renal function, remission of proteinuria, cardiovascular events and quality of life.

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Background
The prevalences of chronic kidney disease (CKD) and end-stage renal disease (ESRD) are continuously increasing around the world. Recent evidence indicates that the number of incident ESRD patients due to glomerular diseases is increasing [1, 2], and many additional ESRD cases are expected to have been attributed to glomerular diseases, considering the cases that have not been confirmed by kidney biopsy. However, the discovery of pathognomonic biomarkers and disease-specific therapeutic targets for glomerular diseases is limited.

To better understand the pathophysiology, biomarkers, and treatment targets of glomerular diseases and ultimately to improve clinical outcomes, it is imperative to translate and integrate research with various types of biospecimen linked to deep clinical phenotyping, including clinical information, self-questionnaires, digital pathology and outcomes from the electronic health record (EHR) and administrative data. A significant additional number of kidney disease cohorts were established through several international consortiums. The C-PROBE, [3] ERCB cohort [4] with CKD patients, and Nephrotic Syndrome Study Network (NEPTUNE) cohort [5] for patients with nephrotic syndrome were started in approximately 2010, and these cohorts are relatively small. Recently, large-scale genomics consortia, including CKDGen [6] and EUREnome [7], have been activated in the United States and Europe. However, these cohorts are not sufficient to support data for Asians. To that end, a multicentre prospective cohort based on deep clinical phenotypes, biospecimens, and digital pathology has been established in Korea, the ‘KORNERSTONE’, which is supported by the Korea Centers for Disease Control and Prevention (KCDC).

The objectives of the KORNERSTONE are as follows: 1) establish a collaborative, innovative deep clinical phenotype-based investigational infrastructure to carry out clinical and translational studies of glomerular disease; 2) perform a longitudinal observational cohort study of patients with biopsy-proven glomerular diseases; and 3) gain insight into the pathophysiology, natural history and novel treatment targets of glomerular diseases. In the present paper, we report the KORNERSTONE design and methods in detail.

Methods/design
Ethics statements
The basic protocol of this study was approved by the ethics committee of each participating centre, including the institutional review boards of Seoul National University (1404–117-575), Keimyung University Dongsan Hospital (DSMC 2019–04–015-001), Chung-Ang University (1942–005-369), Severance Hospital (2019–0463-001), Boramae Medical Center (L–2019–126), and Kangwon National University Hospital (KUNH-2019-05-009). Additionally, the ethics oversight committee of the KORNERSTONE reviewed the design and protocols of this study. All of the ethical issues regarding the plans of the KORNERSTONE cohort study will be supervised by this committee.

Study design and population
The KORNERSTONE is a prospective multicentre observational biobank, databank and digital pathology repository of patients with glomerular disease in Korea (NCT 03929887 at [http://www.clinicaltrials.gov]). Nephrologists working in six clinical centres in the major university-affiliated hospitals, pathologists, and paediatricians are participating in this study. Among the six clinical centres, four centres are located in the metropolitan city of Seoul, one is in the southern area, and the last centre is in northeastern Korea.

Patients suspected of glomerular diseases who received kidney biopsy in participating university medical centres are eligible for inclusion in the KORNERSTONE. Patients who previously received a kidney transplant will be excluded. This study will enrol 3000 children (age < 18 years) and adults. Eligible participants will be screened at the inpatient or outpatient clinic of the department of nephrology or paediatrics of each participating hospital. Participants who pass an initial screening and agree to participate will provide written informed consent during their visit. Parents of all children, and children themselves if age more than 6 years, provided written informed consent. Informed consent includes utilization, collection, and provision of demographics, clinical information, and social security number for the linkage of administrative data and biospecimens. When a participant wants to withdraw
from the KORNERSTONE, all stored biospecimens and data will be destroyed or deleted. All of the laboratory data, self-questionnaires and biospecimens will be collected at the time of kidney biopsy for the baseline information (Table 1). Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Sample size consideration
Table 2 summarizes the statistical power for time-to-event analyses (minimum detectable hazard ratio [MDHR]). For illustration, MDHRs were described for comparisons between two groups of equal size, which could represent any subgroups of interest (e.g., genetic risk alleles, treatment exposures, and clinical diagnosis). Clinical outcome event rates, including ESRD, death and complete remission, were based on published articles and early observed data in other glomerular disease cohorts [8–11].

Clinical, patient-oriented outcomes and follow-up
After enrolment, all of the participants will be assessed for whether they reach clinical endpoints each time they visit the outpatient clinic. The clinical endpoints of this study were divided into two categories: 1) deterioration of clinical outcomes was defined by doubling of serum Cr or decrease in estimated glomerular filtration rate (eGFR) by more than 30%, and 2) improvement of clinical outcomes was defined by the remission of glomerulonephritis and proteinuria <0.3 g/day. Other hard outcomes were defined by ESRD, cardiovascular events, and death. The patients who have proteinuria < 0.3 g/day at baseline have no improvement in clinical outcomes.

Whether the enrolled patients reached each clinical endpoint will be confirmed by the EHR. If the participant displays deterioration, improvement of clinical outcomes, ESRD or cardiovascular events, laboratory findings, urinalysis, and biospecimens, including serum, plasma, buffy coat, and urine, will be collected from the participants. Stools will be collected at baseline only. Additionally, the same information and biospecimens will be collected from the participants at least once per year.

In addition, the patient-oriented outcome will be secured by age-appropriate questionnaires. These outcomes will include symptoms from the patient’s perspective, functional status, nutritional status and health-related quality of life. The questionnaires will be collected every year.

All of the administrative data from Statistics Korea, Health Insurance Review and Assessment Service (HIRA) and National Health Insurance Service (NHIS) and ESRD registry data from the Korean Society of Nephrology will be linked through social security numbers or birth date. However, the information will not be stored by the researchers and will only be used for the collection of clinical outcome information under the approved protocol. The prescribed medication and diagnosis defined by the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) will be collected by HIRA and NHIS. The mortality and the cause of death will be obtained from Statistics Korea data. The reached ESRD outcomes, including dialysis and kidney transplantation, will be determined using the data from NHIS and the Korean ESRD registry from the Korean Society of Nephrology (Fig. 1). For clinical hard outcomes, including death and ESRD, the EHR of each participating centre and various administrative data will be used, so the outcome can be reliably determined even in the case of patient transfer to another hospital or of patients who cannot participate this cohort for other reasons.

Electronic health record and questionnaires
The detailed protocol for clinical data and questionnaire collection is described in Table 1. The eligible patients will be evaluated at baseline for demographic information, smoking history, chief complaints, and anthropometric information, including height, weight, and blood pressure. Measurements of the resting blood pressure in the inpatient setting on the kidney biopsy date using an electronic sphygmomanometer will be carried out.

We will collect laboratory findings closest to the kidney biopsy date. Serum creatinine will be measured using an isotope dilution mass spectrometry (IDMS) traceable method. The eGFR will be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for adults. In children younger than 18 years, the creatinine-cystatin C-based CKiD (Chronic Kidney Disease in Children) equation will be used. Blood laboratory tests, such as complete blood cell count; chemistry, including calcium, phosphorus, total protein, and albumin; lipid panel; electrolyte panel; viral serology, and glomerular disease-related serology will be conducted. Quantitative tests of proteinuria and albuminuria will also be carried out. The information on prescribed medication will include the start and end date of each medication, doses per der day, and total number of prescription days.

The subjects will complete age-appropriate questionnaires concerning the quality of life using Kidney Disease and Quality of Life Short Form (KDQOL-SF) version 1.3, socioeconomic status, educational level, physical activity, health behaviours, health care facility utilization, and nutritional status using semi-food frequency questionnaires (semi-FFQs) and a food diary.

Human biospecimen collection, quality control and standard operating procedure (SOP)
Eight types of biospecimens will be collected: plasma, serum, buffy coat, genomic DNA, urine, stools, stool
| Parameters                   | Detailed information | Screening | Baseline | 1 Y | 2 Y | 3 Y | 4 Y | 5 Y | Improvement or deterioration of clinical outcomes | Hard outcomes (ESRD, CV outcomes) |
|------------------------------|----------------------|-----------|----------|-----|-----|-----|-----|-----|-------------------------------------------------|-----------------------------------|
| Informed consent             |                      |           | Y        |     |     |     |     |     |                                                 |                                   |
| Demographic information      |                      |           | Y        |     |     |     |     |     |                                                 |                                   |
| Medical history              |                      |           | Y        |     |     |     |     |     |                                                 |                                   |
| Medications                  |                      |           | Y        |     |     |     |     |     |                                                 |                                   |
| Questionnaires               |                      |           | Y        |     |     |     |     |     |                                                 |                                   |
| Anthropometry                |                      |           | Y        |     |     |     |     |     |                                                 |                                   |
| Blood laboratory findings    |                      |           | Y        |     |     |     |     |     |                                                 |                                   |
| Urine laboratory findings    |                      |           | Y        |     |     |     |     |     |                                                 |                                   |
| Kidney biopsy                |                      |           | Y        |     |     |     |     |     |                                                 |                                   |
| Biospecimens                 |                      |           | Y        |     |     |     |     |     |                                                 |                                   |

CBC complete blood count; KDQOL-SF Kidney Disease-Quality of Life Short Form; PedsQL Pediatric Quality of Life Inventory; AST aspartate aminotransferase; ALT alanine aminotransferase; HCV hepatitis C virus; HIV human immunodeficiency virus; VDRL venereal disease research laboratory test; FANA fluorescent antinuclear antibody; MPO myeloperoxidase; ASO antistreptolysin O; RBC red blood cell; LM light microscopy; IF immunofluorescent; EM electron microscopy; IDMS isotopic dilution mass spectrometry; Cr creatinine; eGFR estimated glomerular filtration rate; Y year
DNA and cDNA from glomeruli and tubules in micro-dissected kidney biopsy tissues (Table 1). Anonymous barcodes will be printed and attached to all samples collected. Additionally, registered information, including the type, quantity, and location of biospecimens, will be uploaded to the web database. All of the samples will be subsequently collected regularly according to the standardized protocol. All of the biospecimens, including plasma, serum, buffy coat, urine, genomic DNA and stool DNA, will be stored at the National Biobank of Korea launched by the KCDC.

Blood will be stored as plasma, serum, buffy coat, and genomic DNA. From one participant in the KORNERSTONE, at least one SST tube and two EDTA tubes with blood (8 cc per tube, total 24 cc), more than 10 cc of urine, more than 1 g in 2 bottles of stool, stool DNA, and at least one core of kidney biopsy tissue will be collected. Blood and urine samples will be centrifuged for 10 min and will be distributed in cryotubes. Serum and plasma will be stored in a liquid nitrogen freezer (−196 °C), and other types of biospecimens will be stored in a deep freezer (−80 °C) (Table 3).

For quality control of biospecimens, 7-digit Standard PRE-analytical Code (SPREC), which encodes pre-processing information of biospecimens, will be assigned for each blood and urine sample [12]. Serum and plasma samples will be visually checked for haemolysis. The protocol for each biospecimen is described in the supplementary section.

**Digital pathology repository**

Kidney biopsy materials from enrolled patients, including glass slides scanned into high-resolution whole slide images, both stained and non-stained; digital images of

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**Table 2** Minimum detectable hazard ratio for time-to-event outcomes

| Outcome                                      | 5-year event rates | MDHR\(^a\) for n = 3000 (1500/group) |
|----------------------------------------------|--------------------|---------------------------------------|
| ESRD                                         | 0.12               | 1.36                                  |
| Death                                        | 0.06               | 1.54                                  |
| Complete remission of proteinuria (< 0.3 g/day)\(^b\) | 0.63–0.97          | 1.14–1.17                             |

*Abbreviations: MDHR minimum detectable hazard ratio; ESRD end-stage renal disease.
\(^a\)MDHR is based on the following assumptions: patient follow-up time of 5 years (ESRD and death); a loss of follow-up rate during 5 years hypothesized total of 10%; 80% power, alpha = 0.05.
\(^b\)Group sizes for time to complete remission of proteinuria excluded one-third of the group that was in remission at enrolment.

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![Fig. 1 Overall schemes of the KORNERSTONE. KORNERSTONE, Korea Glomerular disease Biobank Network; gDNA, genomic DNA; OPD, outpatient; EHR, electronic health record; LM, light microscopy; IF, immunofluorescence; EM, electron microscopy; QC, quality control; VPN, virtual private network.](image)
immunofluorescence and electron-micrographs; and pathologic reports from each centre will be collected and uploaded into the KORNERSTONE Digital Pathology Repository (Fig. 2). A digitizing pathology workflow was developed (HuminTec, Suwon, Korea). All of the glass slides will be scanned by Aperio AT2 (Leica Biosystems, Germany, Wetzlar). These digital image files will be stored centrally in the KreoNET server (Seoul National University Hospital, Seoul, Korea). From this system, high-quality pathology images can be acquired in a user-friendly manner and readily shared with clinicians. Before the data are sent to the central server, the study number is allocated to the pathologic images to enable the linking of pathologic data with clinical data and biospecimens. All of these images will be connected in the web-based database.

**Web-based database infrastructure for integration of all information**

The overall schemes of the KORNERSTONE are described in Fig. 1. All of the laboratory findings, prescribed medications, and results of pathology will be extracted from the EHR through the clinical data warehouse as Excel or csv files to reduce participants’ burden. The extracted files, including laboratory and anthropometric results from each hospital, are automatically converted into a common case-report form through the macro algorithms. When the converted case-report form is uploaded to the database, different variables for each hospital can be standardized to match internal variables in the web database. The electronic web-based database management system was developed (Binarylab, Seoul, Korea). Additionally, the automatic questionnaire response system was developed for this cohort (ONCE Interactive, Seoul, Korea). Through this system, all questionnaires will be implemented using a tablet to allow patients to respond directly, and all responses are automatically stored in the web-based database.

Researchers or clinical research coordinators who want to upload or download data in the web-based database management system should log in only using a virtual private network (VPN) system to protect personal information. VPN accounts are managed by the principal investigator and clinical research associate and are only accessible by KORNERSTONE authorized staff.

**Governance and dissemination policy of the KORNERSTONE**

The purpose of the KORNERSTONE is to provide a foundation for the discovery of new prediction markers of glomerular diseases and the promotion of the utilization of human-derived resources within the legal and ethical regulations. Given the guidelines of future activities, the creation of governance in the KORNERSTONE is crucial. All collection of biospecimens and information and clinical and research activities will be supervised by the independent governance of KORNERSTONE (Fig. 3). Researchers who want to use resources from the KORNERSTONE should contact initially the KCDC (biobank@korea.kr). All of the collected data and biospecimens of the KORNERSTONE can be used only for future studies that are within the perspective of scientific objectives of the KORNERSTONE and that are approved by the Dissemination and Advisory Committee (Fig. 4). Any researchers can submit a study proposal including study objectives and the type of data and biospecimens required to the Dissemination and Advisory Committee of the KORNERSTONE. If a study proposal is approved, a new VPN account will be given to the approved researcher. All of the data will not be

| Table 3 Overview of stored samples per participant in the KORNERSTONE |
|---------------------------------------------------------------|
| **Biospecimen** | **Stored vial** | **Volume and amount** | **Storage temperature** |
|-----------------|----------------|---------------------|----------------------|
| Serum           | 1.8 ml cryogenic vial | Adults: 300 μl x 5 vials | ≤ − 196 °C |
|                 |                 | Children: 100 μl x 4 vials |                |
| Plasma          | 1.8 ml cryogenic vial | Adults: 300 μl x 5 vials | ≤ − 196 °C |
|                 |                 | Children: 100 μl x 4 vials |                |
| Genomic DNA     | 1.7 ml microcentrifuge tube | Adults: Total more than 100 μg, 3 vials | ≤ − 80 °C |
|                 |                 | Children: Total 30 μg, 2 vials |                |
| Urine           | 1.8 ml cryogenic vial | Adults: 1 ml x 5 vials | ≤ − 80 °C |
|                 |                 | Children: 200 μl x 5 vials |                |
| Buffy coat      | 1.8 ml cryogenic vial | Adults: 200 μl x 2 vials | ≤ − 80 °C |
|                 |                 | Children: 100 μl x 2 vials |                |
| Stool DNA       | 1.7 ml microcentrifuge tube | 100 μl, 1 vial | ≤ − 80 °C |
| Stool           | 30 ml container  | 1 g, 2 bottles       | ≤ − 80 °C |
| Microdissected glomerulus (cDNA) | 1.7 ml microcentrifuge tube | Total 70 ng x 2 vials | ≤ − 80 °C |
| Microdissected tubulointerstitium (cDNA) | 1.7 ml microcentrifuge tube | Total 100 ng x 2 vials | ≤ − 80 °C |
Fig. 2 Digital pathology repository. LM, light microscopy; IF, immunofluorescence; EM, electron microscopy

Fig. 3 KORNERSTONE governance structure. KORNERSTONE, Korea Glomerular disease Biobank Network; DB, database; KCDC, Korea Centers for Disease Control and Prevention
accessible, as only information and biospecimens from those patients who meet the inclusion criteria in the approved protocol will be provided to the investigators. The results of each study will be reviewed by the Scientific Assessment Committee of KORNERSTONE and will be published after peer review.

Discussion
Glomerular diseases, a set of debilitating and complex clinical disease entities affecting individuals of all ages, are associated with significant mortality and morbidity, including hospitalization and ESRD. Although there are many advances in understanding novel genetic and environmental factors affecting the pathophysiology of various glomerular diseases, there is an insufficient number of basic and translational studies that integrate clinical, pathological, and genetic information. The KORNERSTONE, a prospective cohort study with various biospecimens funded by the KCDC, was established for supporting and providing high-quality clinical information and biospecimens based on deep clinical phenotypes of glomerular diseases.

The presentation and prognosis of each glomerular disease covers a wide spectrum even in the same diagnosis, and it is challenging to define each glomerular disease using only clinical descriptions [13]. This fact might be due to the classification of glomerular disease based on histopathology rather than an understanding of the molecular, genetic or environmental underpinnings of these diseases; thus, kidney biopsy is essential for a definitive diagnosis. However, a kidney biopsy is an invasive, burdensome procedure for patients, so multiple biopsy tissue collections are onerous. Misclassification of the subgrouping of glomerular diseases due to the limited reproducibility of pathologic diagnosis is another barrier for studying glomerular disease [14, 15]. While pathological review is important in diagnosis, progression or remission is identified by clinical phenotypes, including proteinuria or eGFR. Considering the chronic pathway of glomerular diseases, a deep clinical phenotype linked serially to obtained biospecimens will be a complementary substitute for the gap between pathology and clinical phenotype regarding time and precision. Thus, in-depth knowledge of each of these glomerular diseases is needed to provide effective care for the patients. Based on this background, many researchers agreed that the practice of personalized and precision medicine is necessary for this disease entity [16]. Precision medicine proposes the development of new disease definitions achieved by a multi-layered multi-omics analysis of the disease course [17]. These kinds of studies provide comprehensive information along with the genotype-phenotype continuum, and it is inevitable to establish a systemic biobank that includes well-organized clinical data, evaluation of environmental factors and collection of biospecimens. From this point of view, several prospective observational cohort studies for glomerulonephritis were established: the Toronto Glomerulonephritis Registry, [18, 19] the University of North Carolina Glomerular Disease Collaborative Network, [20, 21] PodoNet, [22, 23], the British Columbia Glomerulonephritis Registry [24], Cure Glomerulonephropathy (CureGN), [25] and the NEPTUNE [5]. In addition, regarding biobanks, the Biobank for the Molecular Classification of Kidney Disease (BMCKD) is underway in Canada [26].

Pathology is a crucial test for the diagnosis and evaluation of prognosis for glomerular diseases. Expertise, abundant
experience and reproducibility are critical to exact diagnostic accuracy. A digital pathology repository will be an essential tool for integrating clinical and pathological information together, and this system was introduced in this study. Through this digital pathology, misclassification for a subgroup of glomerular diseases can be reevaluated by many different pathologists and nephrologists. Additionally, with the advancement of high-resolution scanners, computing power, faster networks and file compression technology to scan glass slides, virtual slides with the digitalization of whole pathologic images have been achieved [27]. The introduction of digital pathology allows clinicians and pathologists to efficiently discuss various pathologic findings, not only text-based information. In addition, the reproducibility of diagnosis has been improved. Artificial intelligence that was utilized mainly in radiology and cardiology has been extended to pathology through digital glass slides. Advances in digital pathology and computer-aided diagnostic tools have made it possible for pathologists and nephrologists to identify unique imaging markers related to specific diseases, which leads to improvement of early detection and selection of effective treatment targets [28]. In line with this background, the KORNERSTONE will integrate digital pathologic images.

The KORNERSTONE will collect data from all patients undergoing kidney biopsy due to suspected glomerular disease, which is not limited to a specific diagnosis. Therefore, this cohort will be composed of more diverse diseases, including minimal change disease, focal segmental glomerulosclerosis, membranous nephropathy, membranoproliferative glomerulonephritis, crescentic glomerulonephritis, IgA nephropathy, and lupus nephritis, than the CureGN [25] and NEPTUNE cohorts [5]. Most of the glomerular disease cohorts have been constructed in Western countries. However, the epidemiology of glomerular diseases is different from that in Western populations, [11, 29] so the KORNERSTONE will be a good resource for providing Asian population data and revealing regional variation in glomerular diseases. Additionally, several studies reported that environmental factors and the microbiome can affect the development and prognosis of glomerular diseases, especially in IgA nephropathy [30–32]. The NEPTUNE cohort collected only quality of life and self-reported health data through questionnaires as patient-centred outcomes, and there were no surveys on influential factors other than outcomes. In the KORNERSTONE, environmental factors, including dietary data will be collected using semi-FFQ and food diaries, and stool samples will be gathered for further analysis of the microbiome. This approach will allow many researchers to evaluate in additional detail the impact of environmental factors on glomerular diseases.

One of the strong points of this cohort, administrative data from various government institutions, including HIRA, NHIS, Statistics Korea and the ESRD registry, linked by social security number will be collected. In particular, Korea achieved nationwide health insurance covering its whole population in 1989 [33], and all medical billing data for the total Korean population is included in NHIS and HIRA data. Researchers can achieve full inspection of clinical hard outcomes. Through this method, it is possible to identify all of the clinical outcomes even when the outcomes occur in other hospitals and for patients not enrolled in the clinical centre. Last, after the enrolment, each time the participant visits the hospital, we will check whether they reached the clinical outcomes. Even if there is no event, we collect clinical data and biospecimens every year. Through this follow-up plan, all of the clinical outcomes will be confirmed as soon as possible, and small differences will be detected that are clinically meaningful. Importantly, we can collect diverse and serial biospecimens. In this regard, it is possible to perform further analysis for risk factors of a rapid deterioration of renal function and refine the natural course of each glomerular disease.

In conclusion, we describe the objectives and clinical protocol for the KORNERSTONE. As the first large-scale glomerulonephropathy cohort study with the integration of clinical data, biospecimens and digital pathologic images in Korea, the KORNERSTONE will help to clarify the natural course, complication profiles, and novel treatment targets of the Asian population with glomerular disease. We expect that the KORNERSTONE will promote collaborative research for treatment targets for improving clinical and patient-oriented outcomes in patients with glomerular disease.

Supplementary information
Supplementary information accompanies this paper at https://doi.org/10.1186/s12882-020-02016-z.

Additional file 1. Human biospecimen collection, quality control and standard operating procedure for each biospecimen

Abbreviations
KORNERSTONE: KOrea Renal biobank NEtwork System TOward NExt-generation analysis; complementary DNA, cDNA; CKD: Chronic kidney disease; ESRD: End-stage renal disease; EHR: Electrical health record; KCDC: Korea Center for Disease Control and Prevention; MDHR: Minimum detectable hazard ratio; eGFR: Estimated glomerular filtration rate; HIRA: Health Insurance Review and Assessment Service; NHIS: National Health Insurance Service; ICD-10: International Statistical Classification of Diseases and Related Health Problems-10; IDMS: Isotope dilution mass spectrometry; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; KDOQI-SF: Kidney Disease and Quality of Life Short Form; semi-FFQ: Semi-food frequency questionnaires; SOP: Standard operating procedure; VPN: Virtual private network

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Concept and design: YK, YCK, HGK, HL, and DKK; Writing of manuscript: EK; Acquisition of data: YCK, YK, EYK, NL, YHK, SJL, SH, MC, JHH, SHL, JIP, JTP, BJL, JPL, JNA, HGK, HSL, KCM, KWJ, KHG, SSK, SH, and DLK; Consultation on the questionnaires: DRR, JHK; Critical revision of the manuscript for important intellectual content: YCK, YK, and DKK; Obtained funding: DKK; All authors read and critically revised the manuscript. All authors approved the final manuscript.

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Availability of data and materials
All of the collected data and biospecimens of the KORNERSTONE can be used only for future studies that are within the perspective of scientific objectives of the KORNERSTONE and that are approved by the Dissemination and Advisory Committee.

Ethics approval and consent to participate
The basic protocol of this study was approved by the ethics committee of each participating centre: the institutional review boards of Seoul National University Hospital (1404–117-573), Keimyung University Dongsan Hospital (DSCM-2019-04-015-001), Chung-Ang University (1942–005–369), Severance Hospital (2019–0463-001), Boramae Medical Center (L-2019-126), and Kangwon National University Hospital (KUNH-2019-05-009). Additionally, the ethics oversight committee of the KORNERSTONE reviewed the design and protocols of this study. All of the ethical issues regarding the plans of the KORNERSTONE cohort study will be supervised by this committee. Additionally, the ethics oversight committee of the KORNERSTONE reviewed the design and protocols of this study. Written informed consent will be requested from all eligible patients. Especially, parents of all children, and children themselves if age more than 6 years, provided written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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