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A knowledge representation model for family relationship to three generation

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Abstract:
A system for inputting and storing family information, named “BirThree Enrollment,” was developed to promote a birth and three-generation cohort study (BirThree Cohort Study). In this cohort study, it was necessary to satisfy many operational demands while constantly overwriting and changing input information. Complex kinship information must be quickly and accurately inputed and corrected, and information on those families not yet recruited must be retrieved. For these purposes, many devices are needed, from an input interface to the internal data structure. In the field of genetic statistics, a simple standard expressive form (describe father-child relation and mother-child relation) is used for describing family structure. However, this form doesn't have sufficient information. So we developed a new form in conducting the BirThree Cohort Study. Hence, we expanded the data structure, and constructed the Input control system. Family pedigree information is stored along with initial clinical information, and this enabled the input of all self-reported information to the data base. Operators are able to input this family information before the day is out. As a result, when recruitment is completed, family information will be completed concurrently. Therefore, operators can immediately know certain person's family structure. In this model data correction was improved dramatically, and the system was operated successfully. This study is the first report of the method for storing three generations of family data.

Keywords: Birth cohort, three-generation cohort study, database, kinship, recruit

Background:

The Tohoku Medical Megabank (TMM) Project aims to provide creative reconstruction methods and solve medical problems arising from the Great East Japan Earthquake (GEJE), which occurred in March 2011 [1,2]. In the TMM Project, two prospective cohort studies were initiated in Miyagi and Iwate Prefectures: a population-based adult cohort study called the TMM Community-Based Cohort Study (TMM CommCohort Study) and a birth and three-generation cohort study called the TMM Birth and Three-Generation Cohort Study (TMM BirThree Cohort Study) [3]. For the Comm Cohort Study, the TMM recruited participants at those sites where the specific health checkups of the annual community health examination were performed, at seven Community Support Centers in Miyagi Prefecture, and at five satellites in Iwate Prefecture. For the TMM BirThree Cohort Study, the TMM recruited pregnant women at obstetric clinics and hospitals in Miyagi and Iwate Prefectures along with their children and the children’s siblings, fathers (husbands), grandparents, and other family members. The TMM project contributed to the establishment of an integrated biobank that combines physiological and clinical data with genomics data. Additionally, some of the bio specimens collected by the TMM project were analyzed by other research laboratories, and stored in the TMM database, so as to facilitate a full range of omics analyses [4,5]. In the CommCohort Study, many of the parties concerned were unrelated individuals. Thus, information on kinship relationships was not used for earlier Tohoku Medical Megabank Organization (ToMMo) research, such as the 1KJP reference pane l[6] that used the information collected for the CommCohort Study. They are the results of several preceding studies [7-9] that did not use family information.

In contrast, all of the participants in birth cohort studies were related to other participants. Birth cohort studies were among the first types of research to use data on family relationships. Preceding studies on birth cohorts include LifeLines, ALSPAC, MoBA, DNBC, and BiCCA [10-14]. Some of these studies successfully recruited 100,000 or more pregnant women in the birth cohorts. In these birth cohorts, a primary aim was to follow mothers and their newborns; therefore, recruitment of pregnant women is given priority. There

were few opportunities to recruit additional relatives, and thus the recruitment and enrollment of other relatives was uncommon.
One of the key features of the BirThree Cohort Study is that three-generation cohorts were recruited, rather than just birth cohorts. Therefore, inputting and treating family information is more complex in a three-generation cohort study than in other cohort studies. The Lifelines study positively collects information not only on a pregnant woman and the child, but also on the father and other family members, as much as possible. Thus, it is an important initial research for treating family information. Such family information, however, is stored and maintained by a different system than that used for clinical information. As a result, massive data reduction after recruitment is indispensable, and much work might be needed to maintain the correspondence of clinical information and family information.

As a result, it was necessary to devise a data model to operate the three-generation cohort recruitment. To express kinship information, a common data structure has traditionally been used in the field of statistical genetics [15-17]. Because the traditional data format can describe a parent-child kinship (**Figure** 1A, B), it is necessary and sufficient for drawing family pedigrees and expressing genetic relationships. However, in some large-scale studies, such as the BirThree Cohort Study, this data format is insufficient to meet the various operational demands of three-generation cohort research. For instance, the data format is not sufficient for the enrollment of relatives other than parent-child, such as grandfather-child. Moreover, there are some difficult problems concerning the data operation for the withdrawal of consent. Therefore, it is of interest to describe the basic idea underlying the BirThree Cohort Study and the data model based on the specification. The specification is chiefly organized to handle the following subjects: "Data structure,", "Retrieval," "Consent withdrawal and "Family roles."

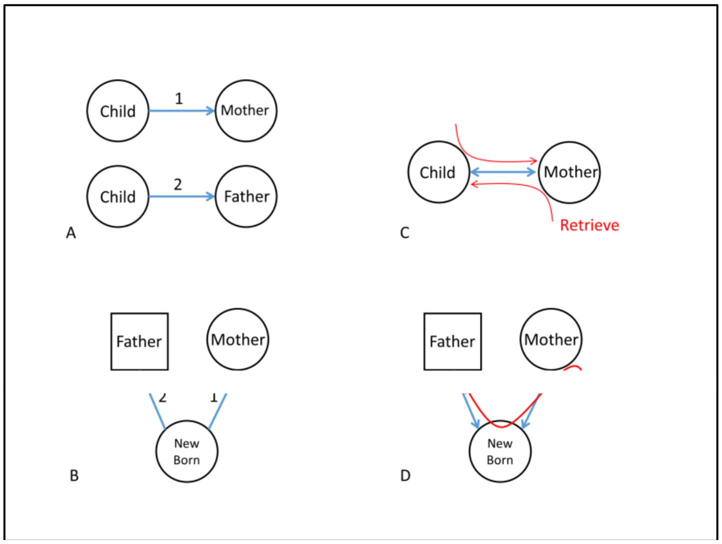


Figure 1: Basic Related Lines describing the relationship between two people. A and B: One-way Related Lines. The child cannot be traced from the mother (or father) by using this line. C. A Bidirectional Related Line, which can be used to trace from a child to a mother and from a mother to a child. D. We can identify the father by tracing the newborn (child) from the mother by using a Bidirectional Related Line.

Materials and Methods:

Bidirectional related line:

The concept of the data model used in typical statistical genetics is described in **Figure** 1A, B. Related Lines 1 and 2 show the relationships between the Child Identification Number (ID) and the Maternal ID or Paternal ID, respectively. These Lines are directional, such that the mother can be retrieved only by the certain child (Related Lines 1), and the child cannot be retrieved by their mother. This structure is used in the kinship2 [18] package in the R statistics program and suffices to describe genetic relationships. There are some problems, however, with retrieving family relationships by using the Related Lines. For instance, to find the child of a certain mother, it is necessary to search all of the children in the database in the worst case scenario. Thus, we first made the Related Line bidirectional (**Figure** 1C). Each related line can thus be defined by two kinds of edges (ex., Child to Mother, Mother to Child) in a direct acyclic graph, rather than one edge in an undirected graph, following a basic idea of network theory [19-21]. With this new bidirectional line, it becomes easier to trace father from mother, by retrieving from mother to child, and from child to father. In this way, relationships between parents are retrieved more quickly (Figures 1B, D). Retrieving all members in the family becomes possible by using this line. One problem of this solution is that the retrieval might become difficult when there is a member who is not participating in the family. We discuss this problem in the following paragraph.

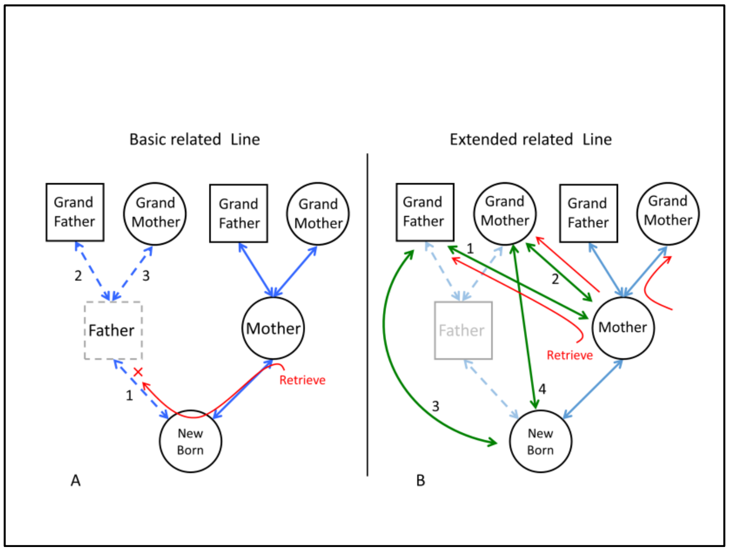


Figure 2: Basic and Extended Related Lines. (A) Basic Related Line only connects the child with the parents. The dotted rectangle shows the family member(s), who have not yet been recruited. When the father is a nonparticipant, a related line is not connected with grandparents by the newborn baby. (B) An Extended Related Line expresses the relationships among seven family members

using many predefined lines. Four extended related lines (green arrow) are selected from among the 21 extended significantly related lines to enroll this family.

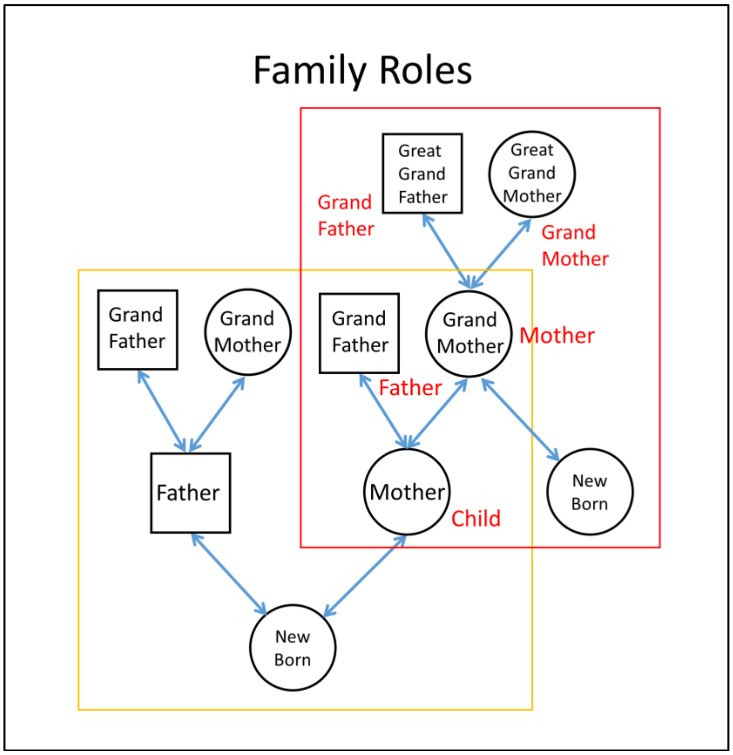


Figure 3: Explanation of family role tables when a participant has two or more family roles.
In this figure, the "mother" in the family role table enclosed within a red rectangle is also a "grandmother" in the family role table within a purple rectangle. When two or more family role tables are applied for one person, it means that the individual has different family roles in each table.

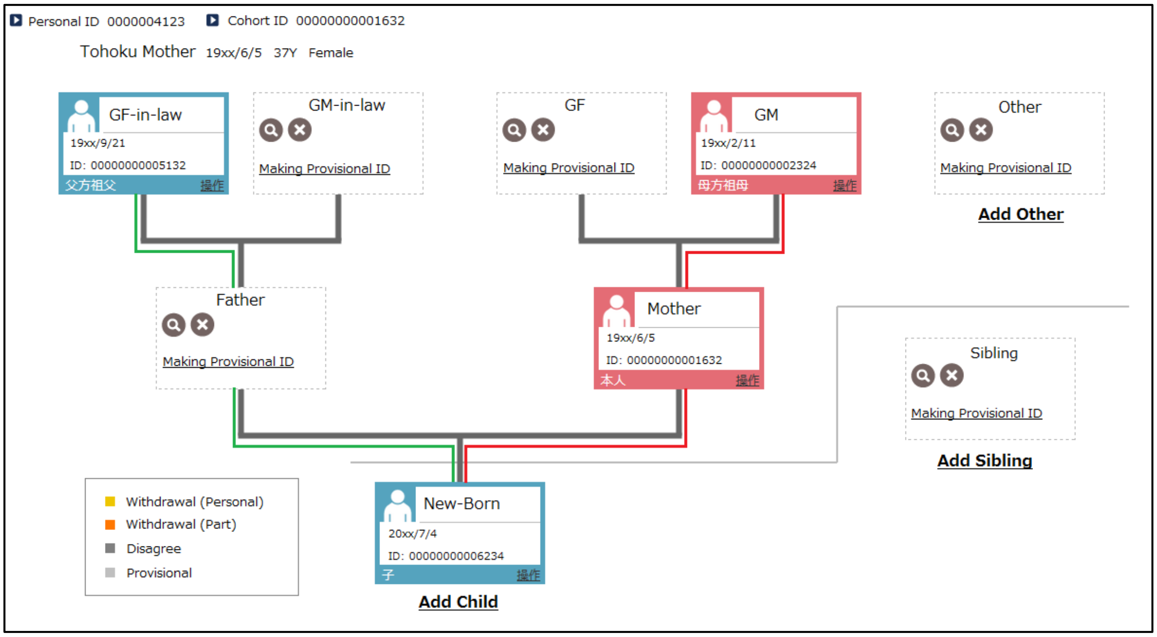
Extended related line:
The necessity for registering the person who doesn't have a parent-child relationship appears, while registering a family's member. One example is that of the relationship between two participants who are connected by a nonparticipant, which is not expressible in bidirectional related line (**Figure** 1). In the case like **Figure** 2A, the relationship between "Newborn" and "Grand-father" cannot be made without the father's participation. One solution to this problem is to define another type of Related Line (the Extended Related Line). This solution is worth adopting according to the cohort study. The Extended Related line connects the relationship from any person in a seven-member family to the other person. Therefore, this line can connect two members in the seven-member family who do not have a parent-child relationship. This approach is thought to work well when the scale of the cohort is small and the lineage is simple. We explain the concept of defining an Extended Related Line for registration below.

According to the inclusion criteria for the TMM BirThree Cohort, pregnant women must be recruited first in a three-generation family. Then, other family members in the three-generation cohort (newborn (child), father, grandmother, grandfather, grandmother-in-law, and grandfather-in-law) are recruited. These seven family members (the pregnant woman and the other 6 family members) are recruited as one unit. In enrolling of a specific participant, it is sometimes necessary to examine other six member's participation status. By means of the bidirectional Related Line, a mother related to a child and the child's father can be retrieved if all three people are participating, as shown in **Figure** 1D. It is impossible, however, to find another family member who is connected through a nonparticipant. For instance, when the husband is not a participant, the grandfather-in-law (paternal grandparent) cannot be enrolled and retrieved from the mother's information by using the bidirectional Related Line (see the red arrow in **Figure** 2A). One solution would be to extend the Related Line to obtain an Extended Related Line. The green arrows in **Figure** 2B show this type of Extended Related Line. Operators can easily find members of the family connected to the pregnant woman and Newborn by using an Extended Related Line. The Extended Related Line offers a method for defining all of the relationships in the cohort. Therefore, the example problem as shown in **Figure** 2A can be solved by defining Extended Related Lines between the mother and grandfather-in-law (green arrow 1), the mother and the grandmother-in-law (green arrow 2), the Newborn and the grandfather-in-law (green arrow 3), and the Newborn and the grandmother-in-law (green arrow 4) (see **Figure** 2B). The relationships between these individuals can be enrolled and retrieved from the mother (a pregnant woman) to the grandparents, or from the Newborn to the grandparents, through Extended Related Lines (**Figure** 2B), even if the father does not participate in the cohort. This idea might work when the data input operator is able to spend sufficient time or when complex family relationships need not be drawn. During the first stage of recruitment of the BirThree Cohort, this idea was adopted for our system, and put into operation. However, we finally stopped using in the system. This is because operation becomes a considerably time-consuming load for the operator. They have to select the proper Line from among 42 types of Extended Related Lines correctly. 42 types of related line mean 21 (Number of combinations. New Born and Grand Father, New Born and Grand Mather ... Grand Father-in-law and New Born) times 2 (bidirectional).

Results:

BirThree Enrollment system:

We have finally developed the BirThree Enrollment system instead of using the system of Extended Related Lines in order to accurately describe complex family roles and avoid the input of incorrect data. It is thought that such a family input system is indispensable to recruit the family members, and this system will become the main current in the Cohort study in the future. The BirThree Enrollment system has a family role table that is used to enroll seven family members. This idea considers two critical factors. One is to apply a pregnant ID, instead of a family ID, to manage the family role table. A pregnant ID is allocated at each pregnancy, while family ID is allocated to the unit of family. A pregnant woman and the number of pregnancies are always identified by a pregnant ID, and the ID is a key to each family role table. The family role table stores seven family member's IDs and their roles. It corresponds to the red or yellow rectangle in Figure 3. By using the pregnant ID, it is possible to recruit members over a long term with stability. On the other hand, a family ID is an idea that comes from the field of genomic analysis. The participants who exist in the same family tree (two or more pregnant women can be included) will have same family ID. It is difficult to manage the Cohort enrolling system by using family ID. Because, after a long period of recruitment, family member will change into a big family, which include two or more pregnant women. Then, the pregnant woman as a proband in the family cannot be identified.



Personal ID 0000004123 Cohort ID 00000000001632

Tohoku Mother 19xx/6/5 37Y Female

GF-in-law
19xx/9/21
ID: 00000000005132
父方祖父 操作

GM
19xx/2/11
ID: 00000000002324
母方祖母 操作

Mother
19xx/6/5
ID: 00000000001632
本人 操作

New-Born
20xx/7/4
ID: 00000000006234
子 操作

Figure 4: Actual family information batch entry screen.

The other factor is the family information batch entry screen, a new family data enrolling method (**Figure** 4). The batch entry screen makes it possible to design a comprehensible data registration interface (see supplemental file). The entry screen not only enables the registration of relationships through nonparticipants, but also facilitates later retrieval and eases registration. A family role table is newly prepared when the pregnant woman is enrolled. At that time, the other six family members are added as provisional participants for whom recruitment is necessary in an empty column (see Section 2.4 **Figure** 4). When some of these six non-participants are recruited and corresponded empty columns are filled, related lines are automatically drawn by the BirThree Enrollment system. As in the example with the nonparticipating father shown in **Figure** 2A, even in the situation whereby a pregnant woman and her father-in-law cannot be connected directly, the Related Lines 1, 2, and 3 in **Figure** 2A among the family members are automatically drawn by our BirThree Enrollment system, and this father is automatically registered as a provisional member. Therefore, lines are always connected whenever family members are retrieved. The family information batch entry screen allows one person to be enrolled in two or more role tables at the same time. As a result, one person can have two different roles in two different families. **Figure** 3 shows a person enrolled as a mother in the family role table enclosed by the red rectangle and as a grandmother in the family role table with the purple rectangle. Such complex expressions are possible in this system. The BirThree Enrollment system was adopted because of this ability.

The system is designed so that each family member is enrolled in a specific position in the screen. At the same time, when a member is enrolled, he or she is also enrolled in the family role table, and the Related Lines between members are automatically connected. The dotted rectangle shows other members of the family who have not yet been recruited. In this figure, "Making Provisional ID" indicates that the member in the rectangle has not yet been recruited. The member is able to be enrolled by pushing the button and issuing temporary ID. Related Lines that correspond to the red line in this figure have already been connected, because the three members (GM (Grand Mother), Mother, New-Born) were already recruited. When "Father" is enrolled, the Related Lines that correspond to the green line will be automatically connected. On the other hand, when "Father" withdraws after participation, the Related Lines corresponding to the green line are kept (not deleted). The number of family members can be increased by clicking the "Add sibling" or "Add Other" button (See the supplementary file).

Implementation:

Figure 4 shows the family information batch entry screen that was used for recruitment in the TMM BirThree Cohort Study. In the implementation, the pregnant woman's ID is treated as the main key, pregnant ID, in the family role table. Therefore, the pregnant woman is always in the family role table. This entry screen is an enrolling screen that is used by the operator during recruitment. All of the positions that the seven family members occupy are created in advance. The family role table corresponds to the entry screen. The input system registers data in both the family role table and the Related Lines. Related Lines are automatically formed for unit members (pregnant woman (mother), newborn (child), father, grandmother, grandfather, grandmother-in-law, and grandfather-in-law). Uncles, aunts, and cousins are also other members of the unit; therefore, operators must draw those Related Lines by hand.

While retrieving the family structure, the database extracts family information by reading only the table of the corresponding family role. Tracing a related line for the retrieval is not necessary. Therefore, the load on the database system is minimized. Moreover, it becomes easy to recruit a related family through the pregnant woman, because the system displays the member who has not yet been recruited in the family.

Withdrawal of Consent:

When a pregnant woman withdraws her consent, the consent of her new born child is withdrawn. On the other hand, other family members (siblings, father, Grandparents) stay as participants in principle, because their consent forms are still effective. Alternatively, they are registered as a participant in the follow-up survey by the TMM Project. In contrast, when a member other than a pregnant woman withdraws consent, only that person's name and information are deleted. For that case, the Related Line containing that person and other members of the family is not deleted, and the family role table remains. For example, when a participating father withdraws his consent, the Related Lines 1, 2, and 3 in **Figure** 2A are maintained to avoid re-recruiting people who have been withdrawn.

Discussion:

We created an input and data registration system, "BirThree Enrollment," for a birth and three-generation cohort study and successfully collected data from more than 70,000 BirThree Cohort participants, which were required for a research platform [10, 22-25]. This system was used by more than 150 BirThree Cohort Genome Medical Research Coordinators (GMRC), and development was advanced to the fifth version. TMM's work is the first attempt in the world to create a three-generation Cohort Study that collects participant data on a 100,000-person scale [26]. Our study was able to achieve the large-scale number of participants, while some other birth cohort studies faced difficulties to collect the aimed numbers of participants, and closed [27]. The operation of this system contributed to the success of the research. From the viewpoint of data science, this work is a method for displaying and browsing a 7-member family tree, and provides the data model required to achieve our Cohort Study [26]. It is practically effective even when a family's information changes dynamically by withdrawal of the agreement. The remaining problems include handling information on a participant who gave birth two times or more and a father who divorced the pregnant woman. Our system was insufficient to decide which data to store for the person who had participated two times or more. The other problem, the "father who divorced," did not actually occur for pregnant women who participated two or more times with a different husband for each pregnancy. It was unnecessary to connect information about the different fathers.

Conclusions:

There are a lot of difficulties to complete a three-generation cohort project with high efficiency, because the process of inputting family information is complicated. To address these problems, computational support is extremely important. In this study, many problems involved with treating family information have been solved with reference to four subjects. We believe that this study to be useful for the next third-generation cohort study.

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This study was conducted in accordance with the Declaration of Helsinki. The authors have no conflicts of interest directly relevant to the content of this article.

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