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Feasibility of identifying families for genetic studies of birth defects using the National Health Interview Survey

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Abstract

Background: The purpose of this study was to determine whether the National Health Interview Survey is a useful source to identify informative families for genetic studies of birth defects.

Methods: The 1994/1995 National Health Interview Survey (NHIS) was used to identify households where individuals with two or more birth defects reside. Four groups of households were identified: 1) single non-familial (one individual with one birth defect); 2) single familial (more than one individual with one birth defect); 3) multiple non-familial (one individual with more than one birth defect), and 4) multiple familial (more than one individual with more than one birth defect). The March 2000 U.S. Census on households was used to estimate the total number of households in which there are individuals with birth defects.

Results: Of a total of 28,094 households and surveyed about birth defects and impairments, 1,083 single non-familial, 55 multiple non-familial, 54 single familial, and 8 multiple familial households were identified. Based on the 2000 U.S. census, it is estimated that there are 4,472,385 households where at least one person has one birth defect in the United States and in 234,846 of them there are at least two affected individuals. Western states had the highest prevalence rates.

Conclusions: Population-based methods, such as the NHIS, are modestly useful to identify the number and the regions where candidate families for genetic studies of birth defects reside. Clinic based studies and birth defects surveillance systems that collect family history offer better probability of ascertainment.

Background

During the past decade, there has been significant progress in identifying the genetic basis of many Mendelian conditions. In February 2003, the Online Mendelian Inheritance in Man catalog reported the localization of 14,206 gene loci, of which 13,311 are autosomal, 792 are X-linked, and 103 are Y-linked or mitochondrial[1]. Some of these have been shown to cause birth defects (i.e., hypohidrotic ectodermal dysplasia, dentinogenesis imperfecta II, Papillon-Lefevre syndrome, Apert syndrome, aniredia, Van der Woude syndrome, popliteal pterygium, and congenital fibrosis of the extraocular muscles). Progress, however, has been substantially slower for the more common disorders that are complex and influenced by multiple genes interacting with each other and with environmental factors. For example, the search for the genetic basis of non-syndromic cleft lip with or without cleft palate (CL/P) began more than 60 years ago (see the classic work of Fogh-Andersen[2]), but despite a relatively high heritability rate for clefts[3], the search for...
susceptibility genes has only yielded weak linkages and inconsistent results [4-6]. This may be due, in part, to the limitations of current linkage strategies as well as our lack of understanding of the role of genetic polymorphisms in response to environmental factors.

Several approaches (ie, linkage analysis, association studies) can be used to identify disease causing or disease predisposing genes [7,8]. Most of them require, or their statistical power greatly benefits from, the use of "multiplex" families (families with two or more affected members). While birth defects surveillance systems are adequate at identifying individual cases, they rarely collect family history. The objective of this study is to determine the utility of the National Health Interview Survey to identify informative families for genetic studies of birth defects.

Methods

The National Health Interview Survey

The National Health Interview Survey (NHIS) is a household survey conducted by the U.S. Bureau of the Census annually since 1957. The NHIS focuses on the civilian, non-institutionalized population in the United States. Each year the NHIS randomly samples approximately 46,000 households with 116,000 members from 201 primary sampling units nationally. In 1994 and 1995, a special two-year Disability Supplement was added to the NHIS to gather nationally representative data on the characteristics, service use, needs, circumstances and experiences of non-institutionalized people with disabilities in the United States.

A subset of the approximately 90,000 households participating in the 1994/1995 NHIS (about 28,000 households) was asked about eligible birth defects including: spina bifida and hydrocephalus, other deformities of the central nervous system, congenital anomalies of the heart and circulatory system, cleft palate and cleft lip, other deformities of the digestive system, congenital dislocation of hip, other congenital anomalies of the musculoskeletal system, and others. Table 1 includes the ICD-9 codes of the conditions included in these categories.

For the purpose of classifying the population by geographic area, the states were grouped into four regions. These regions, which correspond to those used by the U.S. Bureau of the Census, are as follows:

- Northeast: Maine, Vermont, New Hampshire, Massachusetts, Connecticut, Rhode Island, New York, New Jersey, and Pennsylvania.
- Midwest: Ohio, Illinois, Indiana, Michigan, Wisconsin, Minnesota, Iowa, Missouri, North Dakota, South Dakota, Kansas, and Nebraska.

Table 1: Conditions reported in the four groups with birth defects extracted from the NHIS (1994/1995)

| Conditions                                      | ICD-9 Codes | Single Non-Familial n=1,083 (%) | Multiple Non-familial n=115 (%) | Single Familial n=113 (%) | Multiple Familial n=26 (%) |
|------------------------------------------------|-------------|---------------------------------|---------------------------------|--------------------------|--------------------------|
| Spina Bifida and Hydrocephalus                  | 741 (X71.9) | 43 (4.0)                        | 5 (4.4)                         | 7 (6.2)                  | 0 (0.0)                  |
| Other deformities of the central nervous system | 742.2, 4.5.8.9 | 10 (0.9)                       | 2 (1.7)                         | 0 (0.0)                  | 0 (0.0)                  |
| Congenital anomalies of the heart and            | 745 – 747   | 225 (20.8)                      | 18 (15.7)                       | 14 (12.4)                | 7 (26.9)                 |
| circulatory system                              |             |                                 |                                 |                          |                          |
| Cleft palate and cleft lip                      | 749, (X91.9)| 37 (3.4)                        | 5 (4.4)                         | 2 (1.8)                  | 0 (0.0)                  |
| Other deformities of the digestive system        | 750.2 – 9, 751 | 25 (2.3)                       | 0 (0.0)                         | 0 (0.0)                  | 1 (3.9)                  |
| Undescended testicle                            | 752.5       | 4 (0.4)                         | -                               | -                        | -                        |
| Congenital dislocation of hip                   | 754.3 (X75.9)| 11 (1.0)                       | 3 (2.6)                         | 1 (0.9)                  | 0 (0.0)                  |
| Other congenital anomalies of the musculoskeletal system | 754.0.1,756.4-9, (X20 – X29, X33-X35, X70, X73, X74, X76-X78, X93)*** | 573 (52.9)                  | 70 (60.9)                      | 79 (69.9)                | 15 (57.7)                |
| Others                                          | 744.4,748.752.0-4.6-9,753.1-9,757.758.1-9,759.0-6.8 (X30 – X32, X41, X79, X90)*** | 155 (14.3)                  | 12 (10.4)                      | 10 (8.9)                 | 3 (11.5)                 |

*n: number of subjects. *** Includes the 4th digit .9 only.
• South: Delaware, Maryland, District of Columbia, Virginia, West Virginia, Kentucky, Tennessee, North Carolina, South Carolina, Georgia, Florida, Alabama, Mississippi, Louisiana, Oklahoma, Arkansas, and Texas.

• West: Washington, Oregon, California, Nevada, New Mexico, Arizona, Idaho, Utah, Colorado, Montana, Wyoming, Alaska, and Hawaii.

**Individuals**

Individuals with eligible birth defects were identified using the NHIS Core Condition files. Once identified, unique household and person identifiers were created by concatenating the first seven and eight fields, respectively. These identifiers were used to ascertain individuals and families with greater than one birth defect as well as to link other NHIS datasets to obtain personal and household characteristics for comparison.

**Households**

Four groups of households were extracted from the NHIS: 1) single non-familial, which includes a proband with an isolated birth defect and no other family member living in the same household with a birth defect; 2) single familial, which includes a proband and at least one more family member living in the same household, all with an isolated birth defect; 3) multiple non-familial, which includes a proband with more than one birth defect and no other family member living in the same household with a birth defect, and 4) multiple familial, which includes a proband and at least one more family member living in the same household, all with two or more birth defects. The conditions reported by the individuals living in these households are presented in Table 1. Individual and household characteristics were obtained from the 1994/1995 NHIS survey and summarized in Table 2.

### Table 2: Individual and household characteristics of the four groups with birth defects extracted from the NHIS (1994/1995)

|                       | Single Non-Familial n (% of total) | Multiple Non-familial n (% of total) | Single Familial n (% of total) | Multiple Familial n (% of total) |
|-----------------------|-----------------------------------|-------------------------------------|-------------------------------|---------------------------------|
| **Individual Characteristics** |                                   |                                     |                               |                                 |
| Total Number of Individuals | 1,083                             | 55                                  | 113                            | 16                              |
| Mean age               | 33.7                              | 28.3                                | 26.0                           | 29.8                            |
| Males                  | 489 (45.2)                        | 27 (49.1)                           | 51 (45.1)                      | 5 (31.3)                        |
| Ethnicity              |                                    |                                     |                                |                                 |
| Caucasian              | 907 (83.8)                        | 46 (83.6)                           | 90 (79.7)                      | 12 (75.0)                       |
| African-American       | 117 (10.8)                        | 2 (3.6)                             | 6 (5.3)                        | 4 (25.0)                        |
| Other                  | 48 (4.4)                          | 7 (12.7)                            | 17 (15.0)                      | 0                               |
| **Household Characteristics** |                                   |                                     |                                |                                 |
| Total Number of Households | 1,083                             | 55                                  | 54                             | 8                               |
| Mean Family Size       | 3.5                               | 3.5                                 | 4.35                           | 4.0                             |
| Income                 |                                    |                                     |                                |                                 |
| <$10,000               | 77 (7.1)                          | 3 (5.5)                             | 6 (11.1)                       | 2 (25.0)                        |
| $10,000 to <$20,000    | 194 (18.0)                        | 10 (18.2)                           | 8 (14.8)                       | 1 (12.5)                        |
| $20,000 to <$30,000    | 169 (15.7)                        | 9 (16.4)                            | 9 (16.7)                       | 2 (25.0)                        |
| $30,000 to <$40,000    | 129 (12.0)                        | 6 (10.9)                            | 12 (22.2)                      | 2 (25.0)                        |
| $40,000 to <$50,000    | 113 (10.5)                        | 5 (9.1)                             | 4 (7.4)                        | 0                               |
| $50,000 +              | 262 (24.3)                        | 15 (27.3)                           | 13 (24.1)                      | 1 (12.5)                        |
| Below NHIS poverty threshold* | 140 (12.9)                       | 7 (12.7)                            | 9 (16.7)                       | 2 (25.0)                        |
| Highest Education of Responsible Adult Family Member |                                   |                                     |                                |                                 |
| 1 – 8 years (elementary) | 34 (3.1)                          | 1 (1.8)                             | 2 (3.7)                        | 1 (12.5)                        |
| 9 – 11 years (high school) | 89 (8.2)                          | 1 (1.8)                             | 6 (11.1)                       | 2 (25.0)                        |
| 12 years (high school graduate) | 351 (32.4)                       | 17 (30.9)                           | 19 (35.2)                      | 3 (37.5)                        |
| 1 – 3 years (college)  | 281 (26.0)                        | 16 (29.1)                           | 12 (22.2)                      | 0                               |
| 4 years (college graduate) | 177 (16.3)                        | 7 (12.7)                            | 9 (16.7)                       | 0                               |
| 5 + (post-college)     | 148 (13.7)                        | 12 (21.8)                           | 6 (11.1)                       | 2 (25.0)                        |
| Region of Residence    |                                    |                                     |                                |                                 |
| Northeast              | 212 (19.6)                        | 9 (16.4)                            | 10 (18.5)                      | 3 (37.5)                        |
| Midwest                | 218 (20.1)                        | 18 (32.7)                           | 15 (27.8)                      | 3 (37.5)                        |
| South                  | 388 (35.8)                        | 15 (27.3)                           | 14 (25.9)                      | 2 (25.0)                        |
| West                   | 265 (24.5)                        | 13 (23.6)                           | 15 (27.8)                      | 0                               |

*NHIS poverty levels for 1994 and 1995 are based on family size, number of children below 18 years of age, and family income using the 1993 and 1994 poverty levels derived from the August 1994 and 1995 Current Population Surveys.
Table 3: Number of households with at least one person with a birth defect and rates (per 10,000) identified in the NHIS (1994/1995) by area of residence and projection to the total U.S. population in 2000.

|                          | n (rate) | Total Projected U.S. 2000* |
|--------------------------|----------|----------------------------|
| Total Number of Households by Region | 28,094   | 104,706,000                |
| Northeast                | 5,604    | 20,087,000                 |
| Midwest                  | 6,825    | 24,508,000                 |
| South                    | 9,568    | 37,303,000                 |
| West                     | 6,097    | 22,808,000                 |
| Households with single non-familial birth defect | 1,083 (385.5) | 4,036,328                 |
| Northeast                | 212 (378.3) | 759,894                    |
| Midwest                  | 218 (319.4) | 782,820                    |
| South                    | 388 (405.5) | 1,512,705                  |
| West                     | 265 (434.6) | 991,327                    |
| Households with multiple non-familial birth defects | 55 (19.6) | 204,984                    |
| Northeast                | 9 (16.1)  | 32,260                     |
| Midwest                  | 18 (26.4) | 64,636                     |
| South                    | 15 (15.7) | 58,481                     |
| West                     | 13 (21.3) | 48,631                     |
| Households with single familial birth defect | 54 (19.2) | 201,257                    |
| Northeast                | 10 (17.8) | 35,844                     |
| Midwest                  | 15 (22.0) | 33,864                     |
| South                    | 14 (14.6) | 54,582                     |
| West                     | 15 (24.6) | 56,113                     |
| Households with multiple familial birth defects | 8 (2.8)   | 29,816                     |
| Northeast                | 3 (5.4)   | 10,753                     |
| Midwest                  | 3 (4.4)   | 10,773                     |
| South                    | 2 (2.1)   | 7,797                      |
| West                     | 0         | -                          |

*Source: Fields JM, Casper LM. America’s Families and Living Arrangements: March 2000. Current Population Reports, P20-537, U.S. Census Bureau, 2001.

Projections
Prevalence rates were calculated based on the number of households identified in each group and the total number of households asked about these specific conditions (28,094). We did not use a weighting strategy since the purpose of our study was to describe population trends rather than to calculate precise estimates of prevalence as done in other studies using the NHIS[9]. Instead, to estimate the total number of households where there are two or more family members with a birth defect, the prevalence rates calculated from the NHIS were applied to the data of the U.S. Census Bureau report "America’s Families and Living Arrangements, March 2000"[10] (Table 3). This document includes trends about households, families, living arrangements, characteristics of single-parent families, differences in the living arrangements of younger and older adults, and data on unmarried-couple households. A comparison of demographic characteristics between the NHIS and the Census report data confirmed that the NHIS sample is an excellent representation of all U.S. households (Table 4).

Frequencies and unadjusted odds ratios and their 95% confidence intervals were calculated with SAS version 8[11] and Stata version 8[12].

Results
Table 1 shows the number and type of conditions found in the four groups of households. Of a total of 28,094 households surveyed for birth defects and impairments, there were 1,083 single non-familial, 55 multiple non-familial (total of 115 affected individuals), 54 single familial (total of 113 affected individuals), and 8 multiple familial (total of 16 affected people) households. Close to 60 percent of all birth defects in these groups were of the musculoskeletal system, such as musculoskeletal deformities of the skull, face, and jaw (including the sternocleidomastoid muscle); chondrodystrophy; osteodystrophies; congenital scoliosis; clubfoot; and flat foot/congenital fallen arches. The other most common conditions were congenital heart defects (CHD), spina bifida and hydrocephalus, and oral clefts. CHDs were particularly frequent in the multiple familial and in the single non-familial groups (26.9% and 20.8% of all the congenital anomalies in each group, respectively).
Table 2 presents individual and household characteristics of the four groups. No statistically significant differences were found; however, there was a higher percentage of females (68.7%, odds ratio [OR]: 1.8, 95% confidence interval [CI]: 0.7–5.1), of African-Americans (25.0%, OR: 2.8, 95% CI: 0.9–9.0), and of households with lower socio-economic status (<$20,000; 37.5%, OR:1.8, 95% CI: 0.5–6.9) in the multiple familial group. Also, none of the 8 households in this group was located in western states.

Table 3 details the number of households with at least one resident with a birth defect and shows projections for the total number of these households in the United States and by region using the 2000 U.S. Census report. Western states have the highest rate of households including residents with birth defects in two of the four groups, single familial and single non-familial.

Of the 54 households with single familial cases, 39 had two and 5 had three family members with the same condition. One household included a pair of male twins with 47, XYY karyotype. In the remaining 10 households, the affected family members had different types of birth defects (Table 5).

**Discussion**

The objective of this study was to determine whether the National Health Interview Survey is useful in identifying households with families who are informative in the genetic study of birth defects. We used the Survey to estimate the total number of households where these families live by geographical region. It was thought that this information could be used by genetic researchers to target areas where the likelihood of finding these families is greater and to anticipate the needed resources with a better understanding of the scope of the task. Unfortunately, the

Table 4: Comparison of household characteristics between the NHIS (1994/1995) and the U.S. Census of households (2000).

| NHIS Survey 1994/1995 | U.S. Census of Households 2000* |
|-----------------------|---------------------------------|
| Number of households with completed survey | 27,978 | 104,706,000 |
| Income                |                                 |
| <$10,000              | 3,403 (12.2)                     | 9,656,000 (9.2) |
| $10,000 to <$20,000   | 4,788 (17.1)                     | 15,142,000 (14.5) |
| $20,000 to <$30,000   | 4,042 (14.5)                     | 14,128,000 (13.5) |
| $30,000 to <$40,000   | 3,238 (11.6)                     | 12,398,000 (11.8) |
| $40,000 to <$50,000   | 2,452 (8.8)                      | 8,281,000 (7.9) |
| $50,000 +             | 5,174 (18.5)                     | 44,505,000 (42.5) |
| Unknown/Missing       | 4,881 (17.5)                     | 595,000 (0.6) |
| Households Size       |                                 |
| Two members           | 8,811 (31.5)                     | 34,666,000 (33.1) |
| Three members         | 4,634 (16.6)                     | 17,152,000 (16.4) |
| Four members          | 4,063 (14.5)                     | 15,309,000 (14.6) |
| Five members          | 1,979 (7.1)                      | 6,981,000 (6.7) |
| Six members           | 722 (2.6)                       | 2,445,000 (2.3) |
| Seven or more members | 565 (2.0)                       | 1,428,000 (1.4) |
| Age of household members |                             |
| Without members under 1 | 27,480 (98.2)              | 101,281,000 (96.7) |
| With members under 1  | 498 (1.8)                       | 3,425,000 (3.3) |
| Without members under 6 | 25,463 (91.0)              | 87,767,000 (83.8) |
| With members under 6  | 2,515 (9.0)                     | 16,939,000 (16.2) |
| Without members 6 – 11 | 26,388 (94.3)              | 86,203,000 (82.3) |
| With members 6 – 11   | 1,590 (5.7)                     | 18,502,000 (17.7) |
| Without members 12 – 17 | 26,604 (95.1)             | 87,213,000 (83.3) |
| With members 12 – 17  | 1,374 (4.9)                     | 17,493,000 (16.7) |
| Without members under 18 | 22,499 (80.42)            | 66,676,000 (63.7) |
| With members under 18 | 5,479 (19.6)                    | 38,029,000 (36.3) |
| Without members 18 – 64 | 10,959 (39.2)            | 16,760,000 (16.0) |
| With members 18 – 64  | 17,019 (60.8)                   | 87,946,000 (84.0) |
| Without members 65 +  | 22,498 (80.4)                   | 80,429,000 (76.8) |
| With members 65 +     | 5,480 (19.6)                    | 24,276,000 (23.2) |

*Source: Fields JM, Casper LM. America’s Families and Living Arrangements: March 2000. Current Population Reports, P20-537, U.S. Census Bureau, 2001.*
results indicate that the NHIS provide limited useful information to be used in this manner.

We used the Survey, particularly years 1994/1995, because it presented several advantages. The NHIS is a large, representative sample of all U.S. households with an annual response rate greater than 90 percent[13]. These data are collected through a personal household interview conducted by interviewers employed and trained by the U.S. Bureau of the Census according to procedures specified by the National Center of Health Statistics and allows for the identification of households where one or more individuals with birth defects reside and the identification of individuals who have one or more than one birth defect. Furthermore, the addition of the Disability supplement in 1994/1995 resulted in specific birth defects on the condition lists unlike other versions of the survey. These data may also be used to identify various health problems, determine barriers to accessing and using appropriate health care, and to evaluate Federal health programs.

Several limitations of the NHIS might have conspired against its usefulness for the stated objective. The accuracy of the birth defect information has not been validated, there are no objective measurements since data are self-reported or by proxy and isolated conditions can not be studied, since most birth defects are grouped by organ of affection. Also, since many of the questions in the NHIS are predicated on limitation of daily activities, identification of cases is problematic as birth defects cause a range of limitations.

Issues around sampling also limit the usefulness of the NHIS in identifying informative families for genetic studies. Estimates are based on a sample of the population, thus are subject to sampling errors and the information on place of residence is limited to multi-state regions and not available at local levels such as states, counties, or districts. Also, since households were asked to identify conditions from specific grouped lists, we likely only identify families with two or more individuals with birth defects of the same class. Finally, several segments of the population are not included in the sample, such as patients in long-term care facilities, persons on active duty with the Armed Forces (though their dependents are included), and U.S. nationals living in foreign countries.

**Conclusions**

The difficulty to locate multiplex families using the NHIS suggests that population based ascertainment of families with two or more members with the same birth defect is an unrealistic strategy. Alternative strategies are needed to study the genetic contribution to most birth defects. One such strategy is to identify prospective participants in specialty clinics. Another excellent source of data, albeit much more expensive than ascertainment through clinics, are the large, collaborative, multi-state or nationwide studies of birth defects, such as the National Birth Defects Prevention Study [14,15]. In addition to identifying families of interest, these studies collect extensive epidemiological data and DNA samples from which genetic susceptibility and gene-environment interactions can be studied.

**List of abbreviations**

CHD: congenital heart defect

C.I.: confidence interval

C/L/P: cleft lip with or without cleft palate
NHIS: National Health Interview Survey

OR: odds ratio

U.S.: United States of America

Competing interests
None declared.

Authors’ contributions
DFW and VN conceived the study, participated in its design, statistical analysis, and manuscript preparation. Both authors read and approved the final manuscript.

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References
1. Online Mendelian Inheritance in Man (OMIM) 2003 [http://www3.ncbi.nlm.nih.gov/Omim/minstats.html].
2. Fogh-Andersen P: Inheritance of hare lip and cleft palate. Copenhagen: Arnold Busck 1942.
3. Christensen K, Fogh-Andersen P: Cleft lip (+/- cleft palate) in Danish twins, 1970–1990. Am J Med Genet 1993, 47:910-916.
4. Prescott NJ, Lees MM, Winter RM, Malcolm S: Identification of susceptibility loci for nonsyndromic cleft lip with or without cleft palate in a two stage genome scan of affected sib-pairs. Hum Genet 2000, 106:345-350.
5. Marazita ML, Field LL, Cooper ME, Tobias R, Maher BS, Peanchitlertkajorn S, et al.: Genome scan for loci involved in cleft lip with or without cleft palate, in Chinese multiplex families. Am J Hum Genet 2002, 71:349-364.
6. Wyszynski DF: Locating genes for oral clefts in humans. In Cleft Lip and Palate: From Origin to Treatment Edited by: Wyszynski DF. New York : Oxford University Press; 2002:255-264.
7. Lander ES, Schork NJ: Genetic dissection of complex traits. Science 1994, 265:2037-2048.
8. Slagboom PE, Meulenbelt I: Organisation of the human genome and our tools for identifying disease genes. Biol Psychol 2002, 61:11-31.
9. Larson SA, Lakin KC, Anderson L, Kwak N, Lee JH, Anderson D: Prevalence of mental retardation and developmental disabilities: estimates from the 1994/1995 National Health Interview Survey Disability Supplements. Am J Ment Retard 2001, 106:231-52.
10. Fields JM, Casper LM: America’s Families and Living Arrangements: March 2000. Current Population Reports, P20-537, U.S. Census Bureau 2001.
11. SAS Institute Inc. SAS version 8 Cary, NC: 2000.
12. StataCorp. Stata statistical software: Release 8.0. College Station: TX 2003.
13. Adams PF, Marano MA: Current estimates from the National Health Interview Survey, 1994. National Center for Health Statistics Vital Health Stat 10 (193); Hyattsville, MD: Department of Health and Human Services, Public Health Service Publication No. 96-1521; 1995.
14. Yoon PW, Rasmussen SA, Lynberg MC, Moore CA, Anderka M, Carmichael SL, et al.: The National Birth Defects Prevention Study. Teratology 2002, 66:177-184.

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