

# SHARING RESULTS FROM COMPLEX DISEASE GENETICS STUDIES: A COMMUNITY BASED PARTICIPATORY RESEARCH APPROACH

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## ABSTRACT

**Objectives.** Dissemination of research results to communities builds capacity of the community to understand and utilize the results. The objective of this manuscript was to propose a culturally appropriate approach to disseminate complex disease genetics research findings in small Alaska Native communities.

**Study Design.** The Center for Alaska Native Health Research is a community-based participatory research project (CBPR) directed at understanding the interactions between genetic, nutritional and psychosocial risk factors for obesity, diabetes, and cardiovascular disease in Yup'ik Eskimos.

**Methods.** We have consulted with regional healthcare providers, tribal leaders, and university-, local-, and national-institutional review boards to identify potential mechanisms for sharing population-based genetics research results or progress.

**Results.** We propose a six step CBPR-approach to conducting genetics research in isolated identifiable communities. This CPBR-approach includes generating a common research question, determining community interest, recruitment, capacity building, sharing power and control, avoiding group harm, and development of culturally appropriate dissemination procedures.

**Conclusions.** Research scientists and community members should both benefit from population-based genetics research. Although we are just beginning our discussions with regard to sharing genetics research progress and findings, we believe that it is essential move forward as co-researchers in the CBPR enterprise. (*Int J Circumpolar Health* 2007; 66(1):19-30)

**Keywords:** Yup'ik, Eskimo, confidentiality, family-based recruitment, reporting research results, group harm

**The CANHR study overview**

The Center for Alaska Natives Health Research (CANHR) study is a community-based participatory research (CBPR) project focused on identifying current risk factors for obesity, diabetes, and cardiovascular disease in Alaska Natives living in southwest Alaska. The goal of our multidisciplinary and CBPR study design is to assess genetic, nutritional and behavioral risk factors by integrating the knowledge of the Center researchers with the local knowledge of community stakeholders and residents. A detailed description of the organizational development and procedures of the CANHR study has been described elsewhere (1). In order to examine the interrelationships of genetic and environmental risk factors in the overall development of obesity and diabetes, the CANHR study team, local health corporation, and participating communities collaborated on the development of a study involving family-based recruitment and complex disease genetics that involved community input to shape all aspects of the genetics work.

The goal of a CBPR-orientation to research is to involve the community equally in all aspects of research, from design to dissemination of results (2). This approach has resulted from past studies failing to include members of small, identifiable communities in all aspects of the research process, resulting in some communities being unwilling to participate in future research projects (3; 4). Rather than following a top-down, expert-driven model in which the researcher is distinctively empowered to determine research questions, methods, and results, a CBPR design has the advantage of working directly with communities to ascertain their views on how the project should proceed. From this perspective, research occurs as an iterative

process that emphasizes the values of participation, cooperation, and accountability.

A CBPR approach, while rarely used in genetics research, is fundamental to the ongoing success of the CANHR study. Indeed, there are active discussions throughout the scientific community in regard to ethics of population-based genetics research (5, 6), including how genetics studies should be developed in Native communities (7, 8), how family members should be recruited into genetics studies (9, 10), as well as how, and when, genetics study results should be reported back to participants and/or communities (11, 12). In regard to sharing genetics results with participants, the National Bioethics Advisory Commission (NBAC) recommends that genetics results should not be disclosed to participants unless the results have been confirmed; the findings have significant health implications, and treatment, as well as medical counseling is available (13).

Such guidelines, while important, present CBPR studies focused on population-based studies involving genetics of complex diseases with an ethical dilemma. Complex diseases like obesity, type II diabetes, and cardiovascular disease are thought to result from the composite interactions of numerous genes and environmental factors. While population-based research on complex diseases will ultimately lead to enhanced understanding of disease pathogenesis and improved public health, the path to this endpoint is complex and will require years of research from multiple scientific disciplines (14). In the meantime, CBPR researchers' must acknowledge the importance of reporting back to participating communities in a timely manner, while contending with how to conduct complex disease genetics research within a CBPR framework when our research

findings have not been validated, nor conducted in a clinically approved laboratory, and when there is no treatment available. This manuscript focuses on some of the ethical issues surrounding dissemination of complex disease genetics research findings within Alaska Native communities, and how a CBPR framework may address these issues.

### **Ethical issues in the dissemination of complex disease genetic results in a CBPR study**

In general, dissemination of genetic data raises a complicated set of ethical issues. These issues include group harm, discrimination, stigmatization, and privacy. Genetic data obtained from members of isolated populations or identifiable groups is different from data collected from large admixed population groups because it has the potential to harm not only research participants, but also community members not involved in the research project. If genetic results indicate that one population has a higher disease risk, this could lead to stigmatization and discrimination. Therefore, one recommended safeguard to reduce the risk of stigmatization of socially identifiable populations is to withhold the name of those communities in publications or presentations (15). In addition to community protections, scientific investigations must also ensure privacy and confidentiality of individual participants and their family member's such that the ethical principle of beneficence is fulfilled (11).

Within a CBPR framework, an overriding objective is to include the community as an equal partner in the research enterprise. This includes sharing results that are both positive and negative. However, if genetic data do not provide an immediate health benefit to participants, should researchers withhold results?

Perhaps the most reasonable and ethical compromise is to provide genetics research "progress updates" to participating communities, since individual participant feedback does not meet NBAC guidelines. Ultimately, we believe it is essential to determine the communities' views on ethical issues related to dissemination of genetics research progress so that they have an active role in this important decision.

### **CANHR and the CBPR approach**

Employing a CBPR approach, CANHR researchers partnered with ten Native communities to conduct each phase of the study. In addition, the regional Yukon Kuskokwim Health Corporation (YKHC) played an integral role in shaping the overall process, including community recruitment and selection, individual participant recruitment, data gathering protocols, interpreting results, and developing procedures for sharing individual clinical results (1).

### **A CBPR approach to conducting genetics research**

*Step 1: Determining whether communities wanted to participate in a genetics research project.* Unlike other CBPR research undertaken by the CANHR study team, which generated the research questions at the community level, the questions for the CANHR genetics study derived from analyses of epidemiological data and tribal health meetings that expressed concern about the increasing prevalence of chronic diseases. Because our center includes genetics research, we believe it is extremely important for us to provide some form of genetics education to the Alaska Native community leaders and health corporation representatives to assist their decision-

making about participation in the study. At the same time, it was equally important to identify Alaska Native genetics research concerns before initiating data collection.

To open the dialog of genetics research with the community leaders, we consulted with one of our Center's external advisory committee members, Dr. Linda Burhansstipanov, Executive Director of the Native American Cancer Initiatives, Inc. (<http://natamcancer.org/>), who has conducted many genetics education workshops throughout the country to Native American groups. Previously, she developed the Genetic Education for Native Americans (GENA) program and agreed to deliver a two-day (10 hour) workshop to tribal council and community representatives from our Yup'ik Eskimo study population, as well as to relevant ethics and human studies committee representatives from the YKHC. Approximately 40 people participated in the two day workshop. The workshop introduced topics including basic cell and molecular biology, a review of genetic concepts including inheritance, cultural traditions, risks and benefits, and the Human Genome Project, as well as cultural issues related to genetic research, and guidelines for culturally respectful genetic research.

The GENA workshop enhanced community members' understanding of our approach to human genetics and effectively introduced CANHR scientists to the community. It also provided a key opportunity to build rapport through an open dialogue that revealed our genuine respect for Alaska Native culture and our goal to work collaboratively for culturally respectful protocols. Following the workshop, the YKHC board fully embraced the idea of the genetics research project. Indeed, the importance of genetics research was best

summarized by a respected Elder and Emeritus Member of the YKHC Board of Directors when, in agreement, he stated, "I want to eat what my blood tells me to eat." He summarized his interpretation of the genetic research as a vehicle for confirming that his blood had been formed within his culture to resonate with certain foods and could instruct the people about what food would be healthy for them and lead to wellness.

*Step 2: Community selection and participant recruitment.* YKHC medical staff and CANHR scientists met on several occasions to nominate a set of communities that did not overlap with other similar studies taking place in the region. Communities selected were stratified by population size, geographic location (coastal and river, which are thought to be related to types of diet), and religion (Moravian or Russian Orthodox), which are thought to be related to the prevalence of such risk factors as smoking and alcohol consumption). Only those communities that gave community-wide consent participated. To date, ten communities have already participated. Additional communities have approved the CANHR study and have expressed an interest in future participation. While two communities denied participation, one of those two has since agreed to join the study.

*Step 3: Building research capacity within communities.* Following community selection, the CANHR project hired and trained several staff members that have been instrumental to the success of our research center. These local community and regional residents acted as research assistants for all phases of the study. Our field research coordinator

is a registered nurse and has participated in all aspects of organizing data collection and training many of the staff that work directly with participants. Finally, we also hired a bilingual Yup'ik Eskimo research coordinator at the regional level to function as a liaison between the university, the health corporation, and the participating communities. Working together, this research team recruited and enrolled participants, and collected blood, anthropometric, nutritional, physical activity, and psychosocial data. In addition, the team presented the research results back to the communities in both Yup'ik and English.

Overall, the CBPR framework of working closely together throughout each part of the study provided constant checks and rechecks of the study as it proceeded. For example, the community members initiated questions that led to changes in our research. We also raised questions for the community that helped us understand how to conduct our research in culturally appropriate ways. As a result of these ongoing interactions, we endeavored to develop a procedure (described below) for ensuring a balance between the scientific goals of CANHR researchers and the community, and personal goals of Native participants.

*Step 4: Sharing power and control.* There are many reasons why Native American communities are increasingly concerned about participating in genetics research projects (8). Some of the concerns raised when we began to work with Yup'ik Eskimo participants included being over-researched, not hearing from research scientists that previously initiated projects in their communities, fear of testing for drugs, apprehension about the potential for blood sample use that was not approved in the

original study design, and potential for exclusion from medical care or possible stigmatization if a particular disease or mutation was discovered that might be common in the Yup'ik community (group harm). Such concerns are shared by many indigenous communities (7).

Our CBPR approach suggested that we needed to identify local concerns and develop culturally appropriate solutions in collaboration with community members. For example, many of the community and health corporation concerns related to what the CANHR study was going to do with the participant blood samples, and how CANHR scientists were going to report their results to the broader scientific community. We worked with members of our external advisory committee, the University of Alaska Institutional Review Board (IRB), the Alaska Area IRB, the National Indian Health Service IRB, the YKHC human studies committee, and the Alaska Centers for Disease Control Arctic Investigations Program to reach a consensus on how to share power and control over specimens and information. As a result, we jointly developed protocols, consent forms, and identification procedures that adequately detailed our methods of storage and approved use of the collected blood samples. Moreover, since collective stigmatization was of great concern to the YKHC Human Studies Committee, we agreed that any reporting of our research results in the form of abstracts, publications, and presentations would be approved first by the YKHC to protect the individuals and communities participating in our research. Still, in spite of these efforts to share power and do no harm, the best methods to report our genetics research progress to the participating communities remain unclear.

*Step 5: Avoiding group harm and stigmatization.* Inclusion criteria required that participants be non-pregnant and of Alaska Native descent or married to an Alaska Native. If individuals that were not Alaska Native wanted to participate in the research project, they were allowed to do so and they received direct feedback on their blood lipid profiles, body measurements and overall health. However, their data was omitted from further analysis in the broader CANHR study. By restricting our analysis to Alaska Native Yup'ik Eskimos, our results directly relate to what we have learned about Yup'ik Eskimo health. At the same time, however, it is possible for our participants to be more readily exposed to the possibility of "group harm," since Yup'ik Eskimos come from a small region of Alaska and number less than 25,000 people.

The CANHR scientific team has taken several steps to counter the possibility of potential group harm in our studies. First, we spent considerable time consulting with the communities and the health corporation and working with several IRB committees to develop the final CANHR research operating procedures. Second, we have severely limited access to the blood samples and data collected. All research done with existing samples has to be approved by the CANHR Director, the YKHC Executive Board and Human Studies Committee, and if the aims do not directly relate to obesity, all participants must be actively consented for the new study. Finally, before dissemination of any results can proceed to the publication or presentation stage, all research must be approved by the YKHC Human Studies Committee. These procedures were discussed with each tribal council and approved prior to initiation of the research

projects. One of the first lessons we learned in our efforts to maintain group confidentiality is that our study participants preferred to be called "Yup'ik Eskimo," rather than the more broadly defined "Alaska Native" terminology. In addition, they decided that we should not disclose the names of the individual communities, but rather use the more general regional descriptor of southwest Alaska, and Yukon Kuskokwim region.

As the CANHR genetics project is a family-based research project, and even with many protective strategies in place, we had to consider other issues specifically related to genetic studies in isolated communities that involve family members (9, 10). In terms of design, we believe that several characteristics of the Yup'ik Eskimo population structure will facilitate the identification of obesity susceptibility genes. The reduced number of founders, historical bottlenecks, as well as the small population size, and limited admixture should reduce the number of risk alleles contributing to complex disorders like obesity (16, 17). Moreover, the homogenous environment in which our participants reside will facilitate the control of intervening environmental factors (18). Family member participation is facilitated by the fact that the communities we work in are generally less than 500 people in size and many individuals in nearby communities are related to one another.

During the design of the CANHR study, we discussed recruitment strategies with the local health corporation and ultimately agreed to invite everyone in the communities to participate. While our first wave of participant recruitment in the communities ranged from 30-40% of all eligible partici-

pants, we realized we also needed to discuss how family members of enrolled participants (probands) might be invited to participate in the study. While we wanted to avoid placing undue pressure on probands to encourage relatives to participate, we also did not want to introduce bias into our sampling methods from low participation rates (5). We consulted with the YKHC and ultimately decided that the best option to enhance family member recruitment would be to request that probands call their relatives, invite them to participate in the CANHR study, and then we would schedule several return visits to the relevant communities so that we would be available if relatives decided to participate. While other studies have asked probands to contact their relatives and determine if they were willing to be contacted by the research staff regarding participation, the YKHC thought this may put unnecessary pressure on relatives to participate and constitute an invasion of their privacy. The process we used maximized privacy, but also likely reduced participant accrual (10). Nevertheless, protecting the privacy of family members that did not participate is equally important to protecting the privacy of those that did, since non-participants could potentially suffer psychosocial harm, stigmatization, discrimination, and other forms of group harm from being associated with participants in small communities that did participate. The overall objective of our procedures is to protect participants and non-participants equally from potential stigmatization.

*Step 6: Development of culturally appropriate dissemination procedures for clinical results.* Before we could begin to develop

methods to share genetics results, we first developed a process to disseminate clinical results to participants. These results included blood lipids, fasting glucose levels, blood pressure, nutritional status, and physical measurements. At a community level, aggregate results of the clinical biomarkers, physical measurements, behavioral, and nutritional/physical activity project have been shared to maximize distribution of research knowledge among participants.

Once we obtained our first summary results on Yup'ik health, we began to work closely with community members to develop culturally relevant formats in which our research results could be shared and understood by tribal elders and community members. For instance, the request for formats that used cultural symbols rather than bar graphs or pie charts came directly from members of the tribal council in the first community that hosted a dissemination presentation. An example of a research format results slide that we originally presented to the tribal council (Figure 1) is compared to the culturally relevant slide developed in partnership with our community liaisons after feedback from the tribal council (Figure 2). In this example, bar graphs were replaced with a more meaningful diamond pattern design that is commonly found on traditional garments worn by community members.

Ultimately, the culturally relevant formats we used could not have developed without our strong relationship with the communities. Indeed, our rapport was such that we invited them to openly criticize our presentations so that we could improve intelligibility and cross-cultural translation. In addition, instead

of presenting the results in English and then translating difficult concepts back to Yup'ik, they requested that all of our presentations be made in Yup'ik by the local coordinator in the presence of at least one CANHR scientist who could assist in answering questions. Feedback from the tribal leaders has been extremely positive with regard to these data-summary presentations, and similar presentations have now been made to the YKHC and the broader community of participants.

**Important considerations in reporting progress from population-based genetics studies**

We have only recently received initial results from the genetics research and must now develop culturally appropriate ways to share our research progress with participating communities. In addition, before meaningful discussions can take place, we also need to identify some of the genetic epidemiological considerations that should be discussed

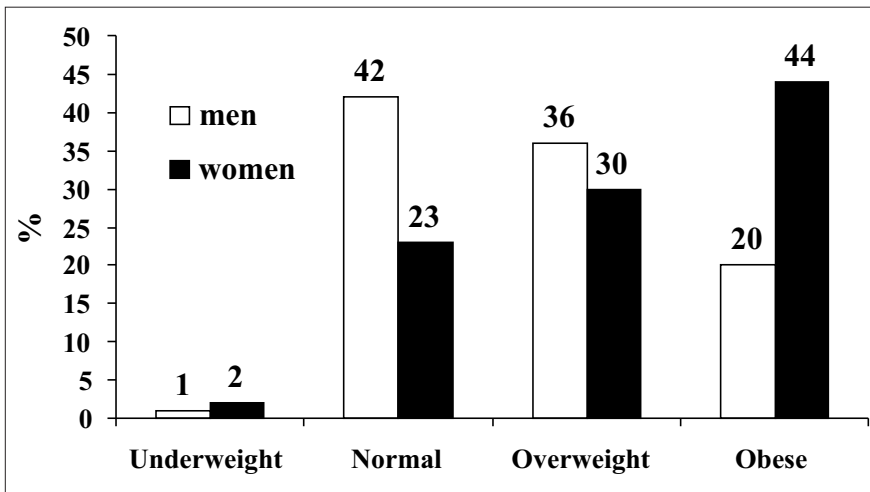


Figure 1. Scientific representation of the prevalence of overweight and obesity in Yup'ik Eskimo men and women. Underweight is defined as a BMI less than 18 kg/m<sup>2</sup>, normal BMI is between 18-25 kg/m<sup>2</sup>, overweight BMI is between 25-30 kg/m<sup>2</sup>, and obese is defined as a BMI greater than 30 kg/m<sup>2</sup>.

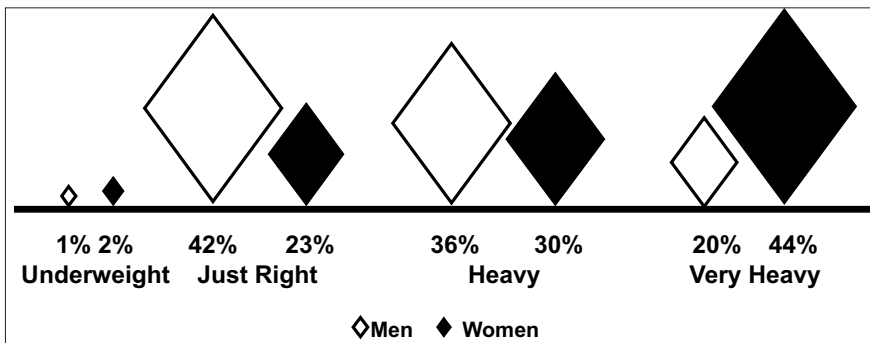


Figure 2. Culturally appropriate representation of the prevalence of overweight and obesity in Yup'ik Eskimo men (n=288) and women (n=352). Underweight is defined as a BMI less than 18 kg/m<sup>2</sup>, just right BMI is between 18-25 kg/m<sup>2</sup>, heavy BMI is between 25-30 kg/m<sup>2</sup>, and very heavy is defined as a BMI greater than 30 kg/m<sup>2</sup>. Mann-Whitney: p<0.001.

with our community partners. The long-term objective of these discussions is to maximize benefit and understanding of genetics research and our progress, while minimizing harm to participating individuals and communities and adhering to the guidelines of the National Bioethics Advisory Commission. These objectives will foster a trusting research partnership with participating communities.

Before discussing genetics research progress with our participating communities, we will first prepare a traditional scientific presentation and share this presentation with CANHR investigators and staff, including Yup'ik Eskimos employed by CANHR. Next we will modify the presentation of research progress based on feedback from CANHR investigators before presenting the revised progress report to, and holding discussions with, our rural community research assistants. Suggested modifications from our rural community research assistants will be incorporated into the revised presentation, and then we will hold a focus group meeting in one of our participating communities to ascertain their understanding of the genetics progress report and incorporate suggestions to improve it. Based on all of the aforementioned feedback, a final presentation format for all future presentations will be developed that will incorporate community views on how genetics results should be disseminated in a culturally appropriate and understandable manner.

Population-based genetics studies similar to the ongoing CANHR study involve genotyping participant samples for genetic variation (polymorphisms) that may be associated with the particular disease of interest. Population-based research studies investigating genetic variation associated with complex diseases

is significantly different from genetic testing for Mendelian abnormalities in clinical laboratories that are approved by Clinical Laboratory Improvement Amendments (CLIA), or reporting lab results from standard clinical practice. In population-based studies like those conducted in CANHR, the genetic tests are conducted solely for research purposes and are conducted in non-CLIA approved research laboratories to identify genetic risk factors for obesity. Results we obtain will need to be replicated in other populations and could only be moved from research to clinical use after their diagnostic, prognostic, and treatment value have been established (12). Once a genetic test is approved for clinical use, the National Bioethics Advisory Commission has recommended that the results should only be disclosed to individuals when: (1) the findings are scientifically valid and confirmed; (2) the findings have significant implications for the subjects health; (3) a course of action or treatment is available; and (4) appropriate medical advice (genetic counsellor) or referral is provided (13).

In general, the immediate clinical utility of population-based genetics studies involving complex diseases like obesity and diabetes are not currently at the stage where a genetic test will result in an improved health outcome (criterion 3 above), and, therefore, from an ethical point of view, the results should not be reported to individuals (19). Nevertheless, in a community-based participatory research model, it is necessary to communicate some form of study progress back to participants, and there may be several reasons to do so, including the fact that relationships between researchers and participants are strengthened (20), participants' understanding of genetics is

improved (21), and trust in the research process may be enhanced if participants are informed of the study outcomes and their contribution to public health (8).

While there are several advantages to sharing genetics research progress with participants, there are also several steps that need to be taken before genetic tests can be used to predict health outcomes (12, 14, 22). First and foremost, the descriptive epidemiology and genetic associations must be replicated in representative populations. Second, the relationship between genotypes and health outcomes for most common diseases is strongly influenced by environmental factors that must be evaluated. Third, a thorough assessment of the analytic validity (test accuracy), clinical validity (how well the test predicts the outcome), and clinical utility (how useful the test is in preventing disease), of complex disease gene testing must be determined in clinical trials and epidemiologic studies (14). Finally, the ethical, legal and social implications of genetic testing must be assessed. Despite these significant hurdles, great strides are being made in this exciting new era of human genome epidemiology (23, 24). Indeed, there is tremendous potential to develop public health interventions based on the identification of environmental factors (behavioral, nutritional, and psychosocial) that may reduce the risk of developing certain diseases.

## Conclusions

### **Beyond collaboration to co-researchers**

Both scientific researchers and community members will benefit from open discussions

related to human research participation in general, and to genetics research participation in particular. From our experiences thus far, many important questions have emerged. How do relatively small identifiable communities view research risks? How do they evaluate research outcomes and their potential for group benefit versus participation in research and the possibility for group harm? Do various communities have specific cultural concerns in relation to genetics research that may be resolved through mutual education, discussion, and trust? How do they resolve personal interests in participation versus community or leadership opposition to participation? What sense do they make of the results that we have obtained? In the end, we will work through interpreting genetic data with community members within our CBPR framework.

While there are many considerations to take into account with respect to reporting genetics results or study progress from population-based studies, in the spirit of CBPR research, we believe it is essential to initiate discussions with our community partners – our co-researchers – on the issues surrounding dissemination. How we ultimately report study progress in genetics research to the community demands that they not only grasp our understanding of the results, but also work with us to make translatable sense of them. An explanation of the uncertainty of complex disease genetics results, the need for replication studies, and the fact that a genetic association does not equate to disease causality is essential knowledge to share. Perhaps preparation of culturally meaningful summary results or progress reports would be helpful, but only after the community has assisted us in interpreting the results. This includes

understanding the importance of negative or inconclusive findings. Although such results may not be exciting to the community, we believe that we should work through these issues together.

Within its infrastructure, CANHR has developed two core facilities to oversee the development of a successful methodology for this co-researcher interaction. The Cultural-Behavioral/Intervention Core and the Genetics Core collaborated on the initial genetics education workshop as well as in understanding how Yup'ik culture perceives blood, genetic transmission, and the appropriateness of reporting research findings. We are in the process of planning how the two cores will engage in the future in a series of workshops and seminars with the Elders and leaders of the communities to address each question and to reach consensus on a Yup'ik ethics of genetics research. Our current objective is to do this in the context of understanding the results that we are now obtaining, to interpret the data together, and to decide, as co-researchers, the best way to disseminate these findings.

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