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Report on:
Stem Cell Legislative Study

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SPECIAL INTERIM COMMITTEE STUDY
HUMAN CLONING

February 2, 2007

SCOPE OF STUDY

The Kansas Health Policy Authority was tasked by the Legislative Coordinating Council to:

1. Study the characteristics of the different types of cloning and various terms used for these types of research (cell cloning, therapeutic cloning, reproductive cloning) and the status of current generally accepted scientific terminology, using as a foundation the *Report of the President's Council on Bioethics, Human Cloning, and Human Dignity: An Ethical Inquiry, Washington, D.C., July 2002*, as well as terminology used by the National Academies of Sciences and National Institutes of Health.
2. Study the national guidelines for stem cell research recommended by the National Academies of Science.

KHPA MISSION

The mission of the KHPA is to develop and maintain a coordinated health policy agenda that combines effective purchasing and administration of health care with health promotion oriented public health strategies. The powers, duties, and functions of the Kansas health policy authority are intended to be exercised to improve the health of the people of Kansas by increasing the quality, efficiency, and effectiveness of health services and public health programs. Because this study falls outside the area of expertise of KHPA Authority staff, this study is concise and specifically follows the direction set by the Legislative Coordinating Committee.

TASK 1. TYPES AND TERMINOLOGY OF CLONING

The scientific literature contains numerous definitions of complex scientific terms related to cloning. Variation in terminology and definitions from the National Institutes of Health, National Academies of Sciences and the President's Council on Bioethics as contained in the different scientific texts can be seen from the table below. Similar terminology has been grouped together to provide for more convenient comparison. Definitions for terms have been included in the table as described in each of the three texts. If the text did not include a specific definition, the corresponding section in the table has been left blank.

TERMINOLOGY TABLE

Term	National Institutes of Health	National Academies of Sciences: Guidelines for Human Embryonic Stem Cell Research	Report of the President's Council on Bioethics, Human Cloning, and Human Dignity: An Ethical Inquiry

Stem Cell	Cell with the ability to divide for indefinite periods in culture and to give rise to specialized cells.	A cell that has the ability to divide for indefinite periods in vivo or in culture and to give rise to specialized cells.	Stem cells are undifferentiated multipotent precursor cells that are capable both of perpetuating themselves as stem cells and of undergoing differentiation into one or more specialized types of cells.
Adult Stem Cell		An undifferentiated cell found in a differentiated tissue that can renew itself and (with limitations) differentiate to yield the specialized cell types of the tissue from which it originated.	
Somatic Stem Cell	Non-embryonic stem cells that are not derived from gametes (egg or sperm).		
Somatic Cell		Any cell of a plant or animal other than a germ cell or germ cell precursor.	A diploid cell containing forty-six chromosomes obtained or derived from a living or deceased human body at any stage of development.
Embryo	In humans, the developing organism from the time of fertilization until the end of the eighth week of gestation, when it is called a fetus.	An animal in the early stages of growth and differentiation that are characterized by cleavage, laying down of fundamental tissues, and the formation of primitive organs and organ systems; especially the developing human individual from the time of implantation to the end of the eighth week after conception, after which stage it becomes know as a fetus.	1. The developing organism from the time of fertilization until significant differentiation has occurred, when the organism becomes know as a fetus. 2. An organism in the early stages of development.
Embryonic Stem Cell	Primitive (undifferentiated) cells derived from a 5-day preimplantation embryo that have the potential to become a wide variety of specialized cell types.	Primitive (undifferentiated) cells derived from the early embryo that have the potential to become a wide variety of specialized cell types	
Embryonic Germ Cell	Pluripotent stem cells that are derived from early germ cells (those that would become sperm and eggs). Embryonic germ cells (EG cells) are thought to have properties similar to embryonic stem cells.	Cells found in a specific part of the embryo or fetus called the gonadal ridge that normally develop into mature gametes. The germ cells differentiate into the gametes (oocytes or sperm).	

Embryonic Disk		A group of cells derived from the inner cell mass of the blastocyst, which later develops into an embryo. The disk consists of three germ layers known as the endoderm, mesoderm, and ectoderm.	
Embryoid Bodies	Rounded collections of cells that arise when embryonic stem cells are cultured in suspension. Embryoid bodies contain cell types derived from all 3 germ layers.	Clumps of cellular structures that arise when embryonic stem cells are cultured. Embryoid bodies contain tissue from all three germ layers: endoderm, mesoderm, and ectoderm. Embryoid bodies are not part of normal development and occur only in vitro.	
Preimplantation	With regard to an embryo, preimplantation means that the embryo has not yet implanted in the wall of the uterus. Human embryonic stem cells are derived from preimplantation stage embryos fertilized outside of a woman's body (in vitro).		
Blastocyst	A preimplantation embryo of about 150 cells produced by cell division following fertilization. The blastocyst is a sphere made up of an outer layer of cells (the trophoblast), a fluid-filled cavity (blastocoel), and a cluster of cells on the interior (the inner cell mass).	A preimplantation embryo of 50-250 cells depending on age. The blastocyst consists of a sphere made up of an outer layer of cells (the trophectoderm), a fluid-filled cavity (the blastocoel), and a cluster of cells on the interior (the inner cell mass).	Name used for an organism at the blastocyst stage of development.
Blastocyst Stage			An early stage in the development of embryos, when (in mammals) the embryo is a spherical body comprising an inner cell mass that will become the fetus surrounded by an outer ring of cells that will become part of the placenta.
Implantation		The process in which a blastocyst implants into the uterine wall, where a placenta forms to nurture the growing fetus.	

Enucleated Egg		A cell whose nucleus has been removed.	
Nuclear Transfer		Replacing the nucleus of one cell with the nucleus of another cell.	
Totipotent	A totipotent stem cell can give rise to all the cell types that make up the body plus all of the cell types that make up the extraembryonic tissues such as the placenta.		A cell with an unlimited developmental potential, such as the zygote and the cells of the very early embryo, each of which is capable of giving rise to (1) a complete adult organism and all of its tissues and organs, as well as (2) the fetal portion of the placenta.
Gamete	An egg or sperm cell.	A mature male or female germ cell, that is, sperm or oocyte, respectively.	A reproductive cell (egg or sperm).
Haploid Human Cell			A cell such as an egg or sperm that contains only twenty-three chromosomes
Diploid Human Cell			A cell having forty-six chromosomes.
Multipotent Cell	Ability of a single stem cell to develop into more than one cell type of the body.		A cell that can produce several different types of differentiated cells.
Pluripotent cell	Ability of a single stem cell to give rise to all of the various cell types that make up the body. Pluripotent cells cannot make so-called "extra-embryonic" tissues such as the amnion, chorion, and other components of the placenta.	A cell that has the capability of developing into cells of all germ layers (endoderm, ectoderm, and mesoderm).	
Germ Cell		A sperm or egg or a cell that can become a sperm or egg. All other body cells are called somatic cells.	
Zygote		A cell formed by the union of male and female germ cells (sperm and egg).	The diploid cell that results from the fertilization of an egg cell by a sperm cell.

Morula		A solid mass of 16-32 cells that resembles a mulberry and results from the cleavage (cell division without growth) of a zygote (fertilized egg).	
In vitro	Latin for "in glass"; in a laboratory dish or test tube; an artificial environment.	Latin for "in glass"; in a laboratory dish or test tube; an artificial environment.	"in glass"; for example, in a test tube
In vitro fertilization (IVF)		An assisted reproductive technique in which fertilization is accomplished outside the body.	The union of an egg and sperm, where the event takes place outside the body and in an artificial environment.
Embryonic Stem Cell Line	Embryonic stem cells, which have been cultured under in vitro conditions that allow proliferation without differentiation for months to years.		
Fetus	A developing human from approximately eight weeks after conception until the time of its birth.		
Differentiation	The process whereby an undifferentiated embryonic cell acquires the features of a specialized cell such as a heart, liver or muscle cell.	The process whereby an unspecialized early embryonic cell acquires the features of a specialized cell, such as a heart, liver, or muscle cell.	
Undifferentiated	A cell that has not yet generated structures or manufactured proteins characteristic of a specialized cell type.	A cell not having changed to become a specialized cell type.	
Directed Differentiation	Manipulating stem cell culture conditions to induce differentiation into a particular cell type.		
Clone	Generate identical copies of a molecule, cell, or organism 1. When it is used to refer to cells grown in a tissue culture dish, a clone is a line of cells that is genetically identical to the originating cell. This cloned line is produced by cell division (mitosis) of the originating cell. 2. May also refer to an animal produced by somatic cell nuclear transfer.		

Cloned Embryo			An embryo arising from the somatic cell nuclear transfer process as contrasted with an embryo arising from the union of an egg and sperm.
Cloning	See Somatic Cell Nuclear Transfer		
Somatic Cell Nuclear Transfer	A technique that combines an enucleated egg (nucleus removed) and the nucleus of a somatic cell to make an embryo. SCNT is the scientific term for cloning. SCNT can be used for therapeutic or reproductive purposes, but the initial stage that combines an enucleated egg and a somatic cell nucleus is the same.	The transfer of a cell nucleus from a somatic cell into an egg (oocyte) whose nucleus has been removed.	Transfer of the nucleus from a donor somatic cell into an enucleated egg to produce a cloned embryo.
Reproductive Cloning	The goal of reproductive cloning is to create an animal being identical to the animal that donated the somatic cell nucleus. The embryo is implanted in a uterus and develops into a live being.		
Cloning to Produce Children			Production of a cloned human embryo, formed for the (proximate) purpose of initiating a pregnancy, with the (ultimate) goal of producing a child who will be genetically virtually identical to a currently existing or previously existing individual.
Therapeutic Cloning	The goal of therapeutic cloning is to create cells that exactly match a patient. By combining a patient's somatic cell nucleus and an enucleated egg, a scientist may harvest embryonic stem cells from the resulting embryo that can be used to generate tissues that match a patient's body. This means the tissues created are unlikely to be rejected by the patient's immune system.		
Tissue Culture		Growth of a tissue in vitro on an artificial medium for experimental research.	

Cell Culture	Growth of cells in vitro in an artificial medium for experimental research.		
Cloning for Bio-medical research			Production of a cloned human embryo, formed for the (proximate) purpose of using it in research or for extracting its stem cells, with the (ultimate) goals of gaining scientific knowledge of normal and abnormal development and of developing cures for human diseases.
Gene (molecular) Cloning			Isolation and characterization of DNA segments coding for proteins (genes) using carrier pieces of DNA called vectors.
Human Cloning			The asexual reproduction of a new human organism that is, at all stages of development, genetically virtually identical to a currently existing or previously existing human being.

TASK 2. NATIONAL GUIDELINES FOR STEM CELL RESEARCH

In 2005, the National Academies established guidelines for research on human embryonic stem cells (hES).[1] The guidelines do not specifically discuss human reproductive cloning, because the National Academies recommended in 2002 that human reproductive cloning should not be practiced since it was considered dangerous and likely to fail.

The seven specific guidelines focus for human stem cell research focus on:

- the permissible scope of research;
- establishment of institutional embryonic stem cell research oversight committees;
- procurement of gametes, blastocysts or cell for hES generation;
- derivation of hES cell lines;
- banking and distribution of hES cell lines;
- research use of hES cell lines;

- and international collaboration.[2]

The first guideline details what the guidelines cover. The guidelines only cover human stem cells from particular cell sources, including blastocysts[3] made for reproductive purposes and later obtained from in vitro (IVF) clinics, blastocysts made specifically for research using in vitro processes, and somatic cell nuclear transfer into oocytes. This guideline establishes three categories of research dividing them into research that is permissible after current mandated review and notification to the research institution, research that would be permissible after additional review, and research that should not be undertaken. Permissible research after review includes in vitro research using previously derived hES lines if there is documentation of the origins of the line, proper informed consent and evidence of compliance with appropriate review boards. Research falling into the category of needing additional review includes generation of new cell lines, introduction of hES cells into a nonhuman animal at any stage of embryonic, fetal or postnatal development, and research in which the identity of donors could become known to researchers. Research that is considered impermissible includes that involving in vitro culture of any intact human embryo for longer than 14 days or formation of primitive streak[4], and research in which hES cells are introduced into nonhuman primate blastocysts or in which embryonic stem cells are introduced into human blastocysts. The first guideline reminds investigators to conduct themselves in accordance with appropriate professional standards.

The second guideline calls for the establishment of institutional embryonic stem cell research oversight committees (ESCRO) that would oversee all issues related to derivation and use of hES cell lines, review and approve the scientific merit of research protocols, review compliance, maintain cell registries, and facilitate education.

Guideline three focuses on procurement of gametes[5], blastocysts or cells for hES generation and recommends procurement through existing institutional review boards (IRB). The guideline includes requirements for consent for donation from each donor (including items that should be included in the consent process), that there be no payment for donation (except women who undergo hormonal induction to generate oocytes[6] for research should be reimbursed only for direct expenses incurred as a result of the procedure), that the investigator should not be the treating physician, that individuals who oppose the process should be excused from participation, and that there should not be requests to generate oocytes in excess of the number necessary to optimize reproductive success.

The fourth guideline governs derivation of hES cell lines and requires a formal request of the ESCRO committee prior to derivation attempts. The scientific rationale for need must be presented to the committee, along with a demonstration of research team expertise in derivation. There must be strong scientific rationale and investigators must document how they will characterize, validate, store, distribute, and maintain confidentiality of coded or identifiable information associated with any new hES cell lines. There is a prohibition on the transference of any blastocyst or embryo using nuclear transfer to any human or nonhuman uterus or to a culture as an intact embryo for longer than 14 days or until primitive streak development.

Banking and distribution of hES cell lines is governed by the fifth guideline. It proposes that institutions involved in this process ensure informed consent is obtained. It also sets standards for creation of an oversight committee, establishing documentation requirements (including information on the donor, the donor's consent, the IRB approval, culture conditions and cell line characterization), security (including maintenance of privacy, audit trails and delivery of pertinent information to donors), and standard practices and systems (identification of samples, characterization of cell lines, process for expanding, maintaining and storing cell lines, quality assurance and control, establishment of a web site, application review process, tracking process, compliance auditing systems, schedules of charges, intellectual property policies, material transfer or user agreements, liability statements and disposal policies). It also calls for clear distribution criteria.

The sixth guideline governs research use of hES cell lines. The guideline calls for action through ESCRO committees to monitor research. The guidelines provide that documentation of the provenance of all hES cell lines should be maintained including evidence of IRB approvals and adherence to legal and ethical standards. If the research consists of in vitro experiments using established cell lines, review beyond the initial documentation is not

necessary. However for other research, there should be a registry of investigators with documentation of knowledge of the guidelines, establishment of protocols and extensive reviews if any research involves the combination of hES cells with nonhuman embryos or adults, both with review for animal welfare issues and also by the ESCRO for special considerations.

The seventh guideline governs international research and provides a process for governance and application of the guideline protections.

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[1] National Research Council and Institute of Medicine of the National Academies, Guidelines for Human Embryonic Stem Cell Research, 2005 at 97-107
[2] Id.

[3] A blastocyst is a preimplantation embryo of about 150 cells produced by cell division following fertilization.
[4] Primitive streak is the developmental stage where the initial band of cells from which the embryo begins to develop is formed.
[5] A gamete is an egg or sperm cell.
[6] An oocyte is an egg.