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Clinical Methods

Animal models in genomic research: Techniques, applications, and roles for nurses☆

Nicole D. Osier, PhD(c), BSN [a,b], Lan Pham, SN [a], Amanda Savarese, BSN [a], Kendra Sayles, BSN, RN [a,c], Sheila A. Alexander, PhD, BSN [a,d,*]

[a] University of Pittsburgh School of Nursing, Pittsburgh, PA 15213
[b] Safar Center for Resuscitation Research, Pittsburgh, PA 15213
[c] McGowan Institute for Regenerative Medicine, Pittsburgh, PA, 15260
[d] University of Pittsburgh School of Medicine, Pittsburgh, PA 15213

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ABSTRACT

Animal research has been conducted by scientists for over two millennia resulting in a better understanding of human anatomy, physiology, and pathology, as well as testing of novel therapies. In the molecular genomic era, pre-clinical models represent a key tool for understanding the genomic underpinnings of health and disease and are relevant to precision medicine initiatives. Nurses contribute to improved health by collecting and translating evidence from clinically relevant pre-clinical models. Using animal models, nurses can ask questions that would not be feasible or ethical to address in humans, and establish the safety and efficacy of interventions before translating them to clinical trials. Two advantages of using pre-clinical models are reduced variability between test subjects and the opportunity for precisely controlled experimental exposures. Standardized care controls the effects of diet and environment, while the availability of inbred strains significantly reduces the confounding effects of genetic differences. Outside the laboratory, nurses can contribute to the approval and oversight of animal studies, as well as translation to clinical trials and, ultimately, patient care. This review is intended as a primer on the use of animal models to advance nursing science; specifically, the paper discusses the utility of preclinical models for studying the pathophysiologic and genomic contributors to health and disease, testing interventions, and evaluating effects of environmental exposures. Considerations specifically geared to nurse researchers are also introduced, including discussion of how to choose an appropriate model and controls, potential confounders, as well as legal and ethical concerns. Finally, roles for nurse clinicians in pre-clinical research are also highlighted.

1. Introduction and purpose

Animal models have been an important research and teaching tool for thousands of years, and are becoming even more important in the advent of the molecular-genomic revolution (Table 1). While the role of molecular genomics in nursing research and clinical practice is increasingly recognized (Anderson, Alt-White, Schaa, Boyd, & Kasper, 2015; Blix, 2014; Leach, Tonkin, Lancastle, & Kirk, 2016; Schutte, 2006; Seibert, 2014; Umberger, Holston, Hutson, & Pierce, 2013; Williams, Cashion, Shekar, & Ginsburg, 2016), the relevance of pre-clinical inquiry to nursing practice is not always readily apparent. Still, several published articles address how these areas of inquiry are germane to nurses working in both research and clinical practice (Page, 2004; Stanley & Paice, 1997; Tkacs & Thompson, 2006; Witek-Janusek, 2004). Within the broader health science research community, a similar circumstance prevails: the role for nurses in various aspects of pre-clinical research and subsequent translation efforts is often not recognized or fully appreciated. Despite this significant gap in awareness, nurses have a rich history of contributing to pre-clinical research, including serving as: 1) members of the research team, such as principal investigator (PI), co-investigator (Co-I), or consultant; 2) overseers of pre-clinical research to ensure it meets ethical and legal standards; and 3) translators of findings to clinical trials, and ultimately, patient care. Increasing understanding of the genomic underpinnings of health and disease, which is typically rooted in pre-clinical research, enables clinicians to better treat patients via precision medicine initiatives.

The primary purpose of this paper is to address the aforementioned gap by highlighting the varied ways that nurses contribute to pre-

☆ Disclaimer about vocabulary: This article employs some fundamental *genetics* and *genomics* vocabulary, not all of which is thoroughly defined in this text; a glossary of key terms used in this review *(italicized in the text)* is provided (Table 1). For additional clarification of terms, the reader is encouraged to utilize the freely available Glossary of Genetic Terms published by the National Human Genome Research Institute (https://www.genome.gov/glossary/). It is also important to note that "*animal model*" and "*pre-clinical model*" will be used interchangeably, though pre-clinical models also include *in vitro* techniques such as cell culture, which are not covered in this review.

* Corresponding author.
E-mail address: salexand@pitt.edu (S.A. Alexander).

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Table 1
Glossary.

Term	Definition
Allele	A specific version of a given gene. For some genes, there may be one or more allele(s) associated with a change in phenotype (e.g. disease risk) compared to the normal version of the gene (i.e. wildtype allele). For other genes there may be variation as evidenced by two or more alleles in the population, but there are no known resulting differences in phenotype. Note: each individual has two alleles for each gene (because humans have 23 pairs of chromosomes, with one member of each pair inherited from their mother and the other from their father). In some cases, one copy of a particular allele results in the associated phenotype, while in other cases two copies of the allele are needed to produce the phenotype.
Animal model	A non-human animal used to study a clinical problem in biomedical research that shares similar physiological and/or functional characteristics with humans of a particular clinical population. In some instances, the species used is already afflicted by a disease common to humans, and other times, a clinical condition is mimicked in animals as part of the experimental procedures. Animal models are used when a question could not be practically, ethically, or safety studied in humans, and they may lay the groundwork for future clinical inquiry and changes in practice.
Autosomal dominant	A pattern of trait inheritance where the given phenotype results when the individual possesses at least one copy of the associated allele, which exists on one of the autosomes (i.e. a numbered chromosome, not the X or Y chromosome). This is in contrast to autosomal recessive conditions, which require 2 copies of the associated allele for the individual to display the phenotype.
Chromosome	A condensed package of DNA found within the nucleus of a cell. Humans have 46 chromosomes in 23 pairs (with one member of each pair coming from each parent). Other types of animals have different numbers of chromosomes. There are two major types of chromosomes: autosomes (numbered chromosomes; 1–22 in humans) and sex chromosomes (X and Y).
Complementary deoxyribonucleic acid (cDNA)	A laboratory-produced doubled stranded DNA molecule. In the context of animal models, cDNA is often used to modify the genomes of test animals, as is the case when generating a knockin animal.
Deoxyribonucleic acid (DNA)	The scientific name for the molecule that contains the genetic information coding for all the proteins comprising a given organism. DNA molecules are double stranded molecules wound together in the form of a double helix.
Conditional (i.e. inducible) mutation	When a given genotype for a particular gene only results in the phenotype of interest under certain environmental conditions. For example, individuals with sickle cell disease only exhibit symptoms of the condition under restrictive environments (e.g. cold; low oxygen; emotional stress).
Gene	A stretch of DNA encoding some trait or protein of interest. Genes are passed on from parents to offspring in the sperm and egg, which contain chromosomes; each chromosome has many genes along it.
Gene expression	The process of producing a protein using the code contained in the DNA. Each set of 3 DNA bases corresponds to a particular amino acid; consecutive amino acids are strung together as a polypeptide, also known as a protein.
Genome	The full set of genetic information for a given organism. Each cell in the organism possesses the full genome within it, mostly in the nucleus (which contains chromosomes), and to a lesser extent in extra-chromosomal mitochondrial DNA.
Genetics	Using scientific techniques to study a particular gene or set of genes.
Genomics	Using scientific techniques to study the entire genome of an organism as opposed to a single gene or small set of related genes (i.e. genetics).
Genotype	The collection of genes possessed by an individual organism that directs protein production and ultimately affects the individual's observable traits (i.e. phenotype). Note: depending on the context, sometimes the term is used to describe the composition of alleles that an individual possesses for a particular gene in the genome.
Heterozygous	An individual who has two different alleles for a particular gene, having received different versions from their mother and father.
Homozygous	An individual who has two of the same alleles for a particular gene, having received identical versions from their mother and father.
In vitro	A process that happens outside of a living organism. The term literally translates to “in glass” because in vitro experiments often happen in in a Petri dish or test tube.
In vivo	A process that happens inside of a living organism. The term literally translates to “in life” because in vivo processes occur within a human organism or other animal.
Knockin	Use of molecular genomic techniques to add genetic information to an organism. This is often done as part of the effort to humanize a test animal to better mimic a clinical population.
Knockout	Use of molecular genomic techniques to remove genetic information from an organism or make the copy non-functional.
Locus/loci	The physical location of a particular gene or stretch of genetic material along a chromosome. When more than one locus is being referred to, they are called “loci.”
Mouse model	Use of a mouse to study a condition that affects humans; a specific type of animal model.
Nucleotide	The most fundamental building block of genetic material (e.g. DNA). Nucleotides have 3 components, a sugar (ribose or deoxyribose), a phosphate group, and a nitrogen-containing base (adenine, guanine, thymine, cytosine, and uracil).
Pharmacogenomics	The intersection of genomic information and pharmacology. Applications include identifying the correct therapeutic regimen based on a patient's genotype and correlating drug response with genotype.
Phenotype	The traits that can be observed or measured in an individual (e.g. hair color; disease presence/absence; height). The phenotype is produced by the genotype when the gene(s) involved are expressed into protein(s); there may also be an impact of environmental factors (e.g. diet; exercise; sun-exposure) on phenotype.
Strain	A population of test animals that are genetically uniform as a result of inbreeding or genetic engineering.
Substrain	A subpopulation of a strain of test animals, uniquely characterized because they have some distinguishing feature from the parent strain, usually as the result of genetic changes that accumulate over several generations of breeding.
Transgenic	A transgenic animal is one who has had DNA from another source inserted into its genome using laboratory techniques.

clinical research efforts, such as study planning, approval, and conduct, as well as efforts to translate findings to clinical trials and care. A secondary aim is to provide nurse scientists interested in conducting animal research with key considerations relevant to planning and executing animal research studies; in doing so, helpful resources for further information will be highlighted. Though the secondary aim is primarily tailored to a nursing research audience, the information may also be relevant to clinicians in helping them to evaluate the quality of pre-clinical studies. To the authors' knowledge, this is the first publication to focus on a review of *animal models* specifically for nursing research and the roles for nurses engaged in, or otherwise interested in, this type of work.

2. The role of nurses

2.1. Overview of the role of nurses in animal research historically and contemporarily

Since antiquity, the vast majority of animal research has been conducted by physicians or bench scientists with training in a scientific discipline outside of nursing (e.g. Biochemistry; Molecular-Biology; Neuroscience; Anatomy & Physiology). Thus, in 2500 years of documented animal research, nurses represent only a minute fraction of the scientists conducting this type of work. This can be explained partly by the comparatively new nature of the nursing profession broadly and