Effectiveness, Costs, and Results of Collaborative Care Approaches to Optimize Outcomes in

Antibody Replacement Therapy

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MEDICAL EDUCATION RESOURCES

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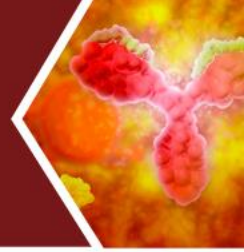
Held in conjunction with AMCP Nexus 2015

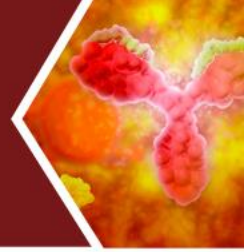
AMCP Academy of Managed Care Pharmacy

Agenda



6:15 AM	Overcoming Barriers to Optimal Antibody Replacement Therapy *Mark Ballow, MD, FAAAAI*
6:45 AM	Pharmacoeconomic Assessment: Considerations to Evaluate the Total Cost of Care *Alan Lyles, ScD, MPH, RPh*
7:05 AM	Managed Care Approaches for Providing Cost-effective Therapy and Improving Patient Outcomes *Jeffrey Dunn, PharmD, MBA*
7:25 AM	Moderated Faculty Panel Discussion and Audience Q&A *Faculty Panel*
7:40 AM	Closing Comments, Post-survey, and Evaluations *Alan Lyles, ScD, MPH, RPh*

Educational Objectives



After completing this activity, the participant should be better able to:

- Characterize the total cost of care for PI, including direct costs associated with drug therapy and associated infections from non-treatment as well as indirect costs, such as those associated with missed work days
- Describe key pharmacoeconomic studies pertaining to Ig replacement therapy and the budgetary implications of these data in a managed care framework
- Characterize the most common payer-driven utilization management strategies for Ig replacement therapy
- Explain how certain management approaches such as site of care mandates, increase member cost-share, and step-therapy requirements adversely impact adherence and outcomes in PI
- Differentiate antibody replacement therapy from other applications of Ig and describe how the differences between IVIG and SCIG may drive the decision of one over the other based on unique patient characteristics
- Characterize the importance of dosing and specifically IgG trough levels in the framework of payer policy and clinical practice for improving outcomes in PI

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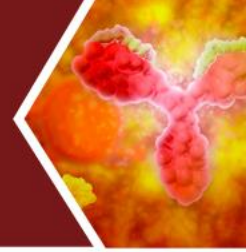
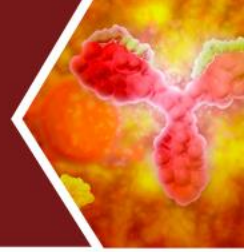


Overcoming Barriers to Optimal Antibody Replacement Therapy

Mark Ballow, MD, FAAAAI
Professor of Pediatrics, Department of Pediatrics
University of South Florida College of Medicine
Division of Allergy & Immunology
All Children's Hospital

Faculty Disclosure

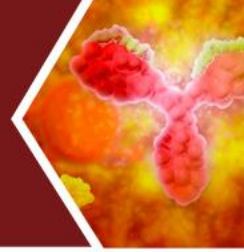


- The ***faculty*** reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:

  Mark Ballow, MD, FAAAAI

  - *Grants/Research Support:* CSL Behring
  - *Consulting Fees:* Baxalta US Inc., CSL Behring
  - *Speakers' Bureau:* Baxalta US Inc., CSL Behring, Grifols

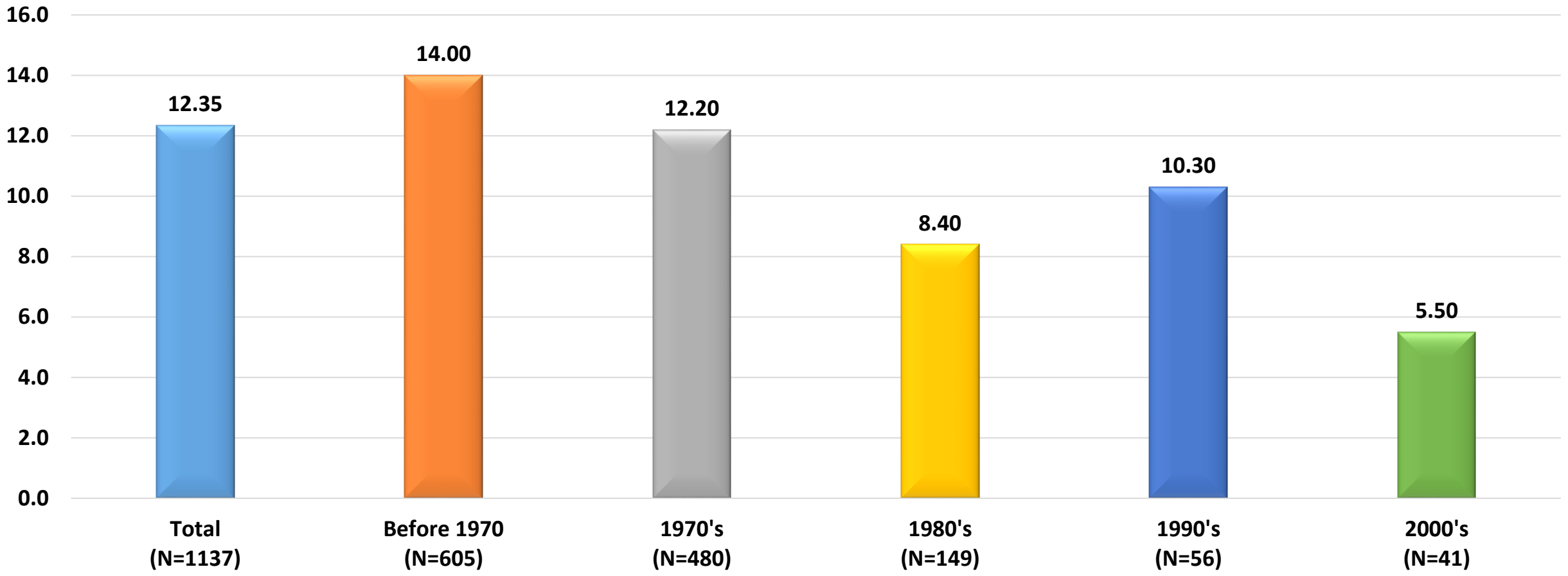
Background/Epidemiology



- Primary immunodeficiency diseases (PI) represent a myriad of life-long conditions that result when a component of the immune system is absent or does not function properly due to a primary or inherited defect
- The International Union of Immunologic Societies and the World Health Organization recognize **more than 250 different PI**
- A 2007 survey of 10,000 households revealed that the prevalence of *diagnosed* PI approaches 1 in 1200 people in the United States or approximately 250,000
  - PI often goes undiagnosed or misdiagnosed
  - The above figure does not take into account individuals with more mild immune system defects who have not been formally diagnosed

Boyle JM, Buckley RH. *J Clin Immunol*. 2007;27:497-50.

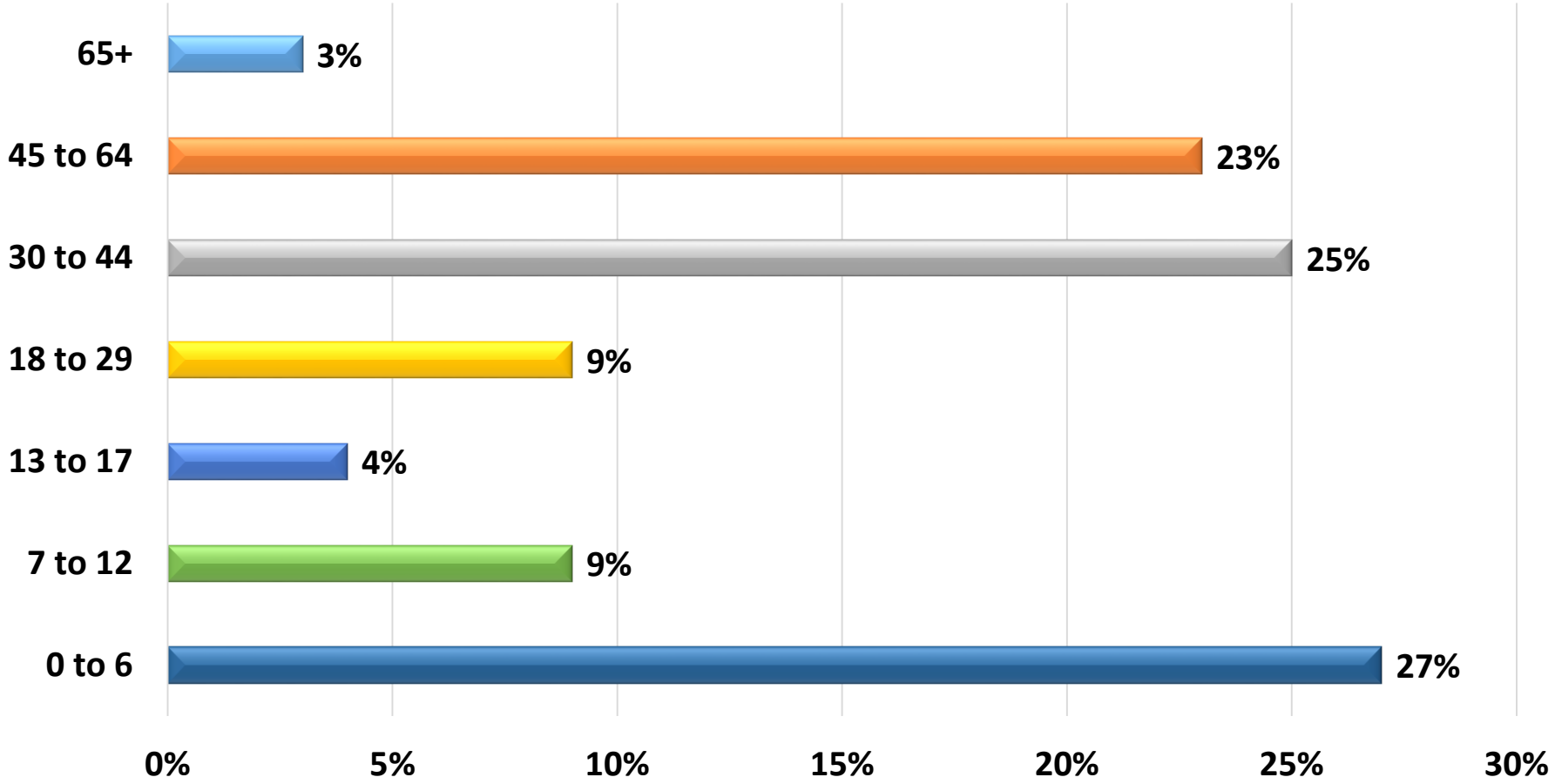
Average Number of Years to Diagnosis by Decade of Diagnosis



Q9. At what age was that person first diagnosed with a primary immunodeficiency disease? Q8. At what age (in years) did these repeated, serious, or unusual infections begin? (Base: Infection prior to diagnosis – N=1,215; 81 cases missing data to Q8 or Q9)

Immune Deficiency Foundation. Immune Deficiency Diseases in America: The Third National Survey of Patients (2007). http://primaryimmune.org/idf-survey-research-center/idf-surveys/patient-surveys/

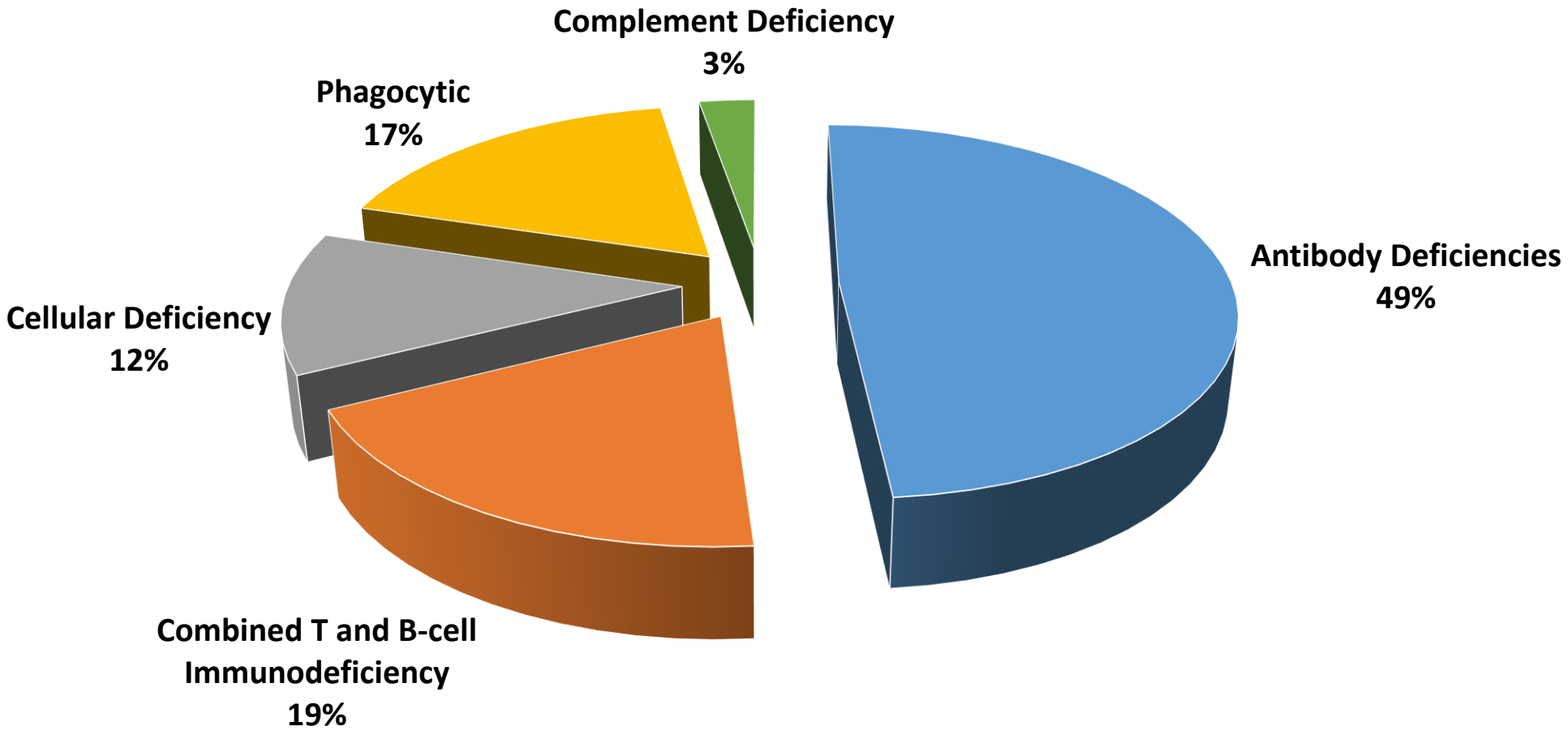
Patient Age at PI Diagnosis



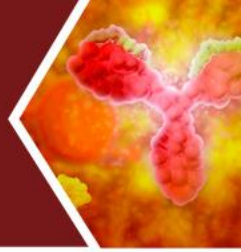
Q9. At what age (in years) was that person first diagnosed with a primary immunodeficiency disease? (N=1,330 – excludes missing data)

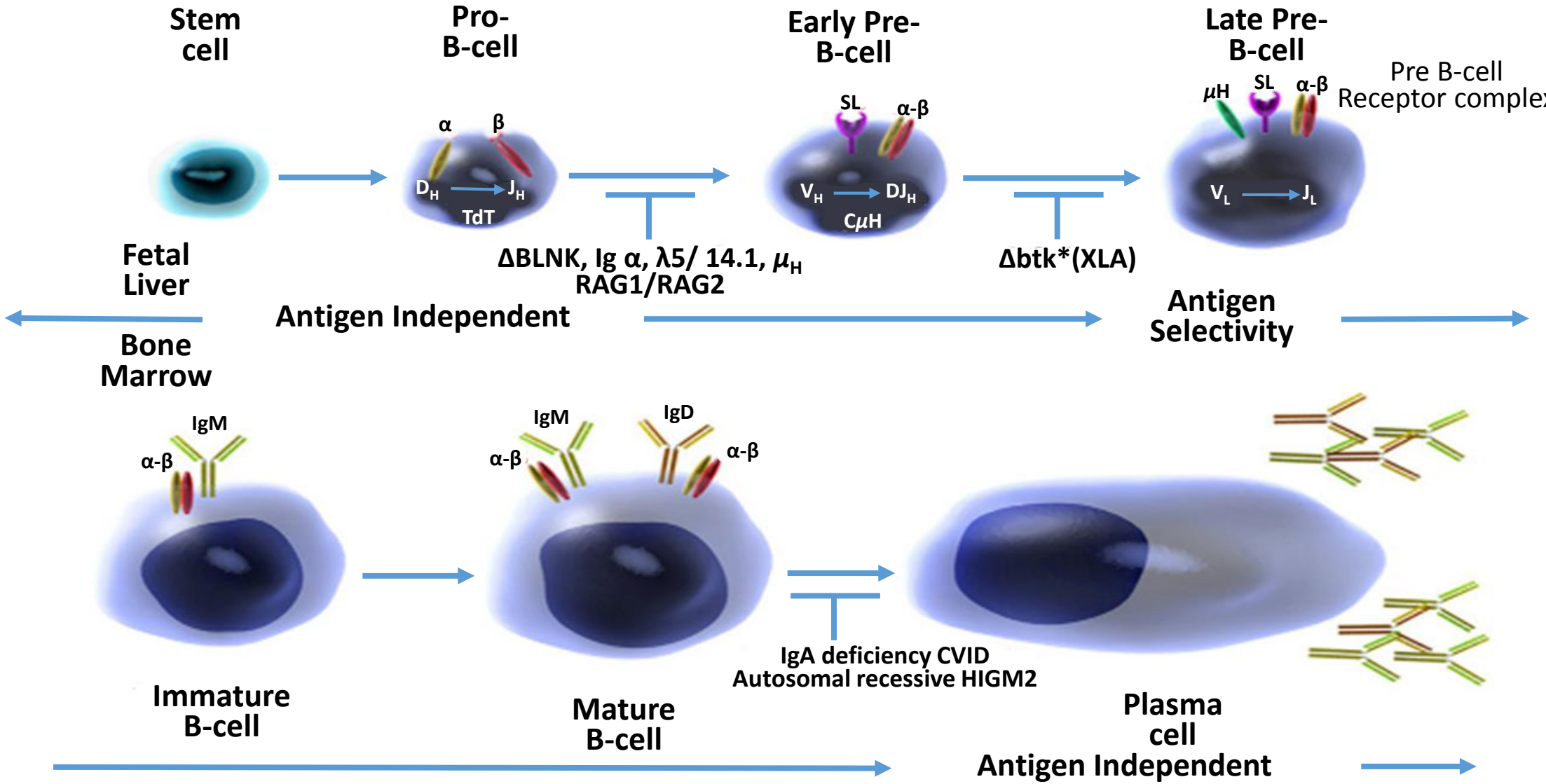
Immune Deficiency Foundation. Immune Deficiency Diseases in America: The Third National Survey of Patients (2007). http://primaryimmune.org/idf-survey-research-center/idf-surveys/patient-surveys/

Relative Distribution of the Primary Immunodeficiencies

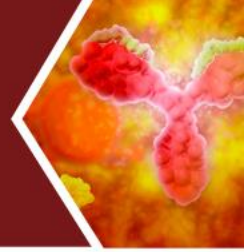


B-cell Differentiation Pathway and Antibody Immune Deficiency Disorders





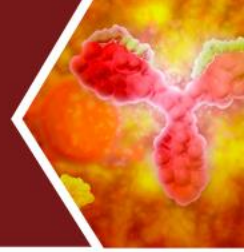
Disease Etiology and Treatment



- Defects in antibody production are the most common type of PI and comprise approximately 60% of such conditions encountered in clinical practice
  - The ***only*** treatment for these patients with antibody deficiencies is ***lifetime*** administration of Ig replacement therapy
- Although approximately 150,000 patients are likely to benefit from Ig replacement, only an estimated 35,000 to 55,000 receive ongoing therapy

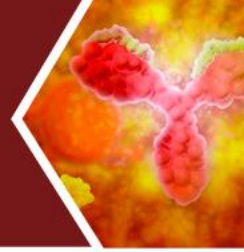
Skoda-Smith S, et al. *Ther Clin Risk Manag*. 2010;6:1–10.

Clinical Characteristics of B-Cell Deficiencies



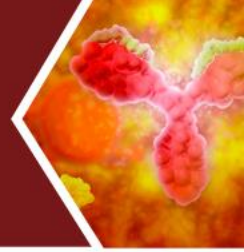
- Onset of symptoms delayed until 7-9 months of age
- Recurrent infections with high grade bacterial pathogens
- Chronic sinopulmonary infections, otitis media, meningitis, sepsis, abscess, osteomyelitis
- Few problems with fungal or viral (except enteroviruses) pathogens

Clinical Characteristics of B-Cell Deficiencies



- No growth failure; survival into adulthood with treatment
- Palpable lymph nodes / nasopharyngeal lymphoid tissues
  - Absent or hypoplasia in Bruton's disease
  - Enlarged in common variable immunodeficiency (CVID)
- Increased incidence of allergy and autoimmune diseases
- Often have GI problems
  - Infection
  - Malabsorption

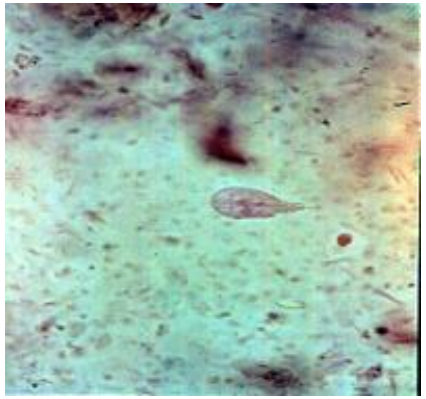
Antibody Deficiency Disorders



- Agammaglobulinemia with absent B-cells
  - Infantile x-linked (Bruton's disease)
    - Tyrosine kinase deficiency
  - Defects of pre-B-cell receptor
  - Defects of B-cell signaling pathway
- Transient hypogammaglobulinemia of infancy
- Isolated immunoglobulin deficiency
  - IgA deficiency
  - IgM deficiency
- X-linked and autosomal recessive forms of Hyper IgM Syndrome
- Common variable immunodeficiency
  - ICOS deficiency
- IgG subclass deficiency
- Selective antibody deficiency with normal immunoglobulins

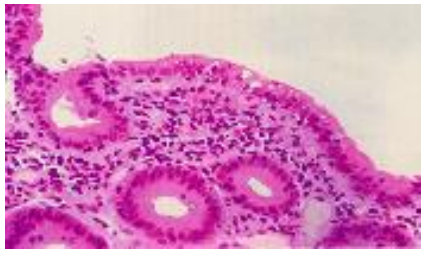
Clinical Findings in CVID

Giardia lamblia infection



- Recurrent sinopulmonary tract infections (73%)
  - Encapsulated organisms
  - Mycoplasma
- Recurrent GI symptoms, chronic GI infection
  - *Campylobacter*/*Salmonella*
  - 10% liver disease
- 1/3 develop lymphoproliferative disorder
  - Intestinal nodular lymphoid hyperplasia
  - Splenomegaly

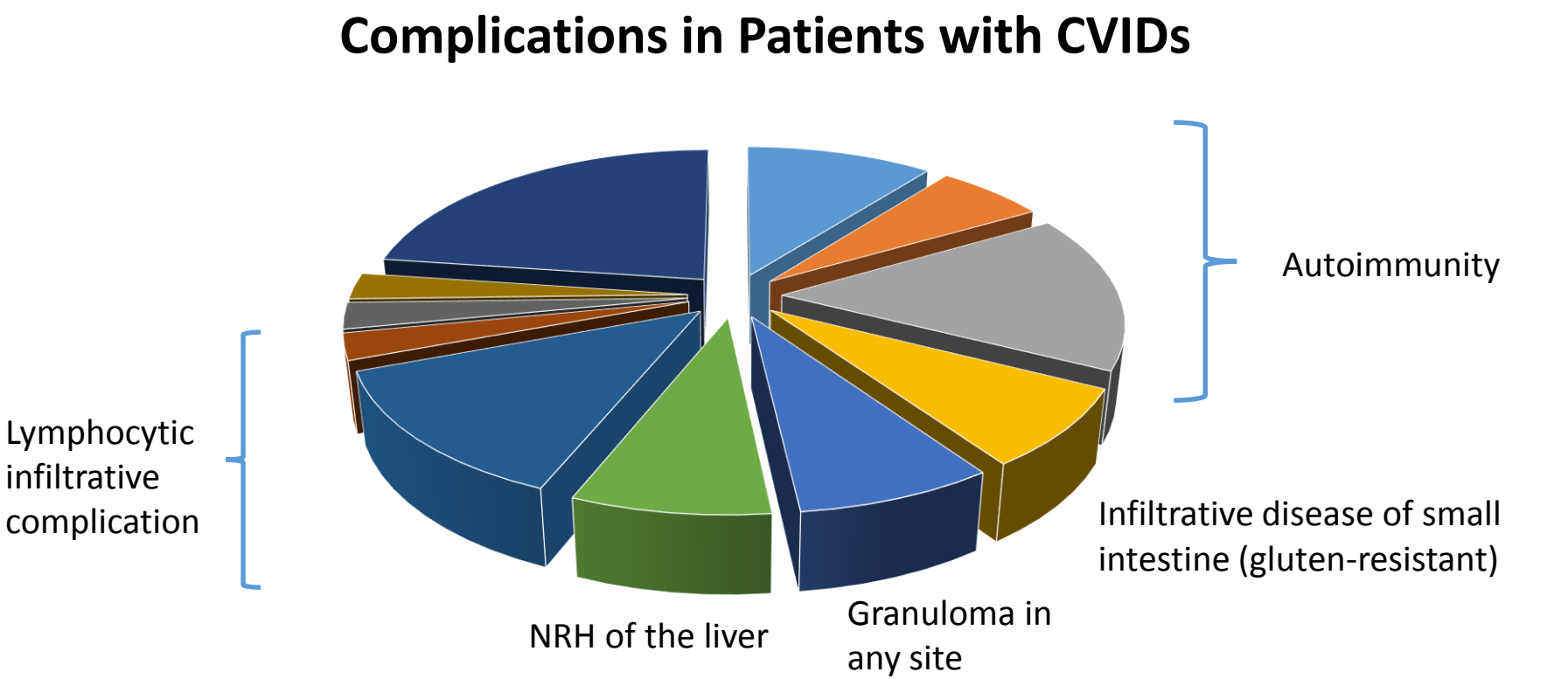
Celiac disease



- Autoimmunity (~25%): PA, celiac disease, ITP, AIHA, systemic rheumatic disease
- Subgroup of CVID have defects in T-cell function
- Increased incidence of non-Hodgkin lymphoma (NHL) and gastric cancer

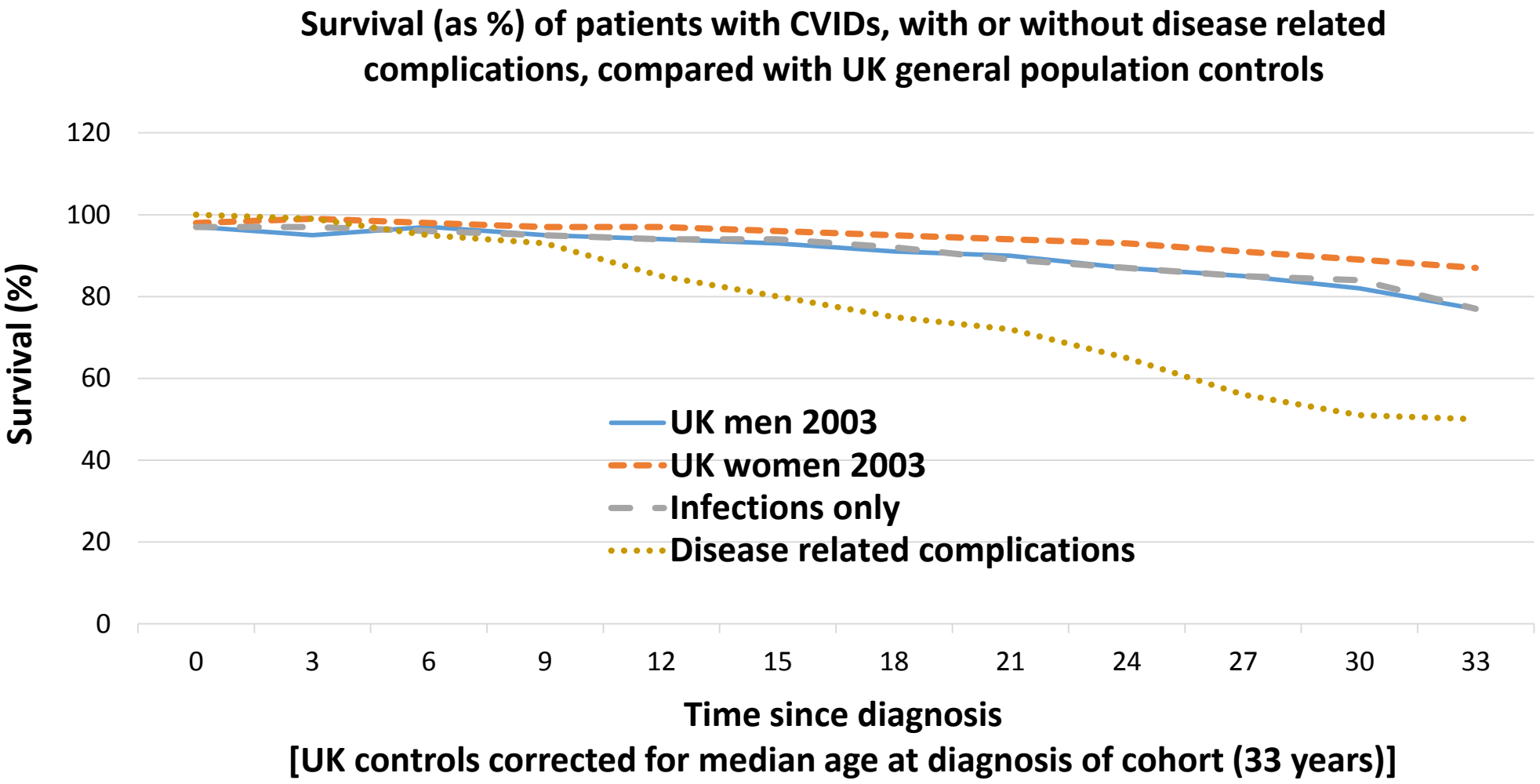
GI=gastrointestinal; PA=pernicious anemia; ITP=idiopathic thrombocytopenic purpura; AIHA=autoimmune hemolytic anemia.

Medical Complications in Patients With CVID



Chapel H, Cunningham-Rundles C. *Br J Haematol*. 2009;145(6):709-727.

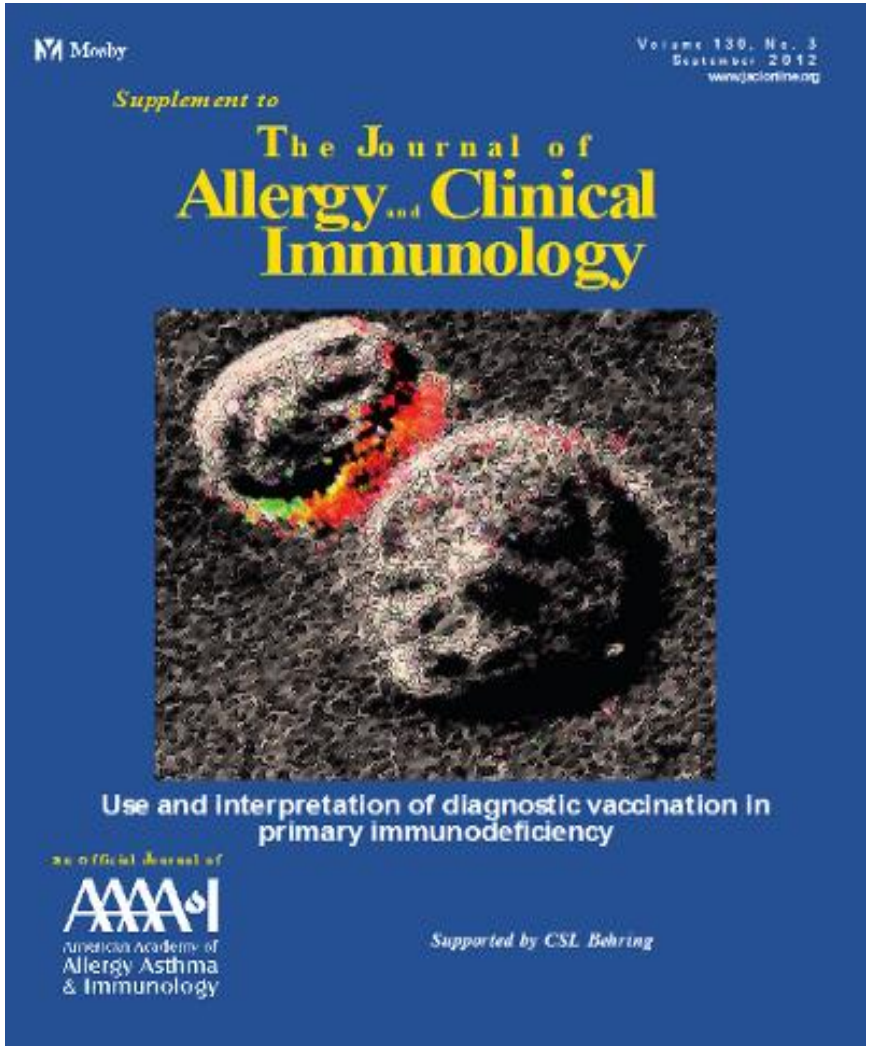
Survival in Patients With CVID



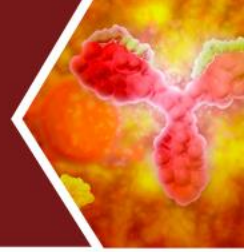
Chapel H, Cunningham-Rundles C. *Br J Haematol*. 2009;145(6):709-727.

Guidelines on the Use of Vaccines in the Evaluation of Patients with Recurrent Infections

- Working group of the AAAAI Basic and Clinical Immunology Interest Section
  - Conceived January 2007 as a joint effort of the Primary Immunodeficiency Committee and Vaccines and Biological Threats Committee
  - Officially charged December 2007
  - Group of 35+
    - 16 primary authors
    - 4 lead authors (Orange, Ballow, Stiehm, Katial)
    - 15 acknowledged contributors
    - Committee members at large



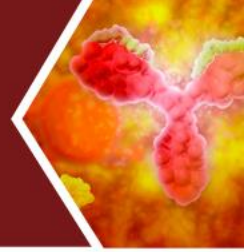
Diagnosis: Immune Functional Analyses



- Immune studies must be performed to demonstrate inadequate levels of Ig and that the patient does not produce specific antibodies in response to infections or immunization
  - Patients with extremely low Ig levels (eg, serum IgG ≤200 mg/dL) are typically excluded from such evaluation
    - "Certain immunodeficiencies are drastic, and pursuing evaluation of humoral immune function through vaccine antigen challenge would delay necessary therapy."
  - Tetanus toxoid, pneumococcal vaccines, and pre-exiting specific antibodies are often used for these immune functional analyses

Orange JS, et al. *J Allergy Clin Immunol*. 2012;130:S1-S24.

I. Use of common vaccines for measurement of humoral immune function

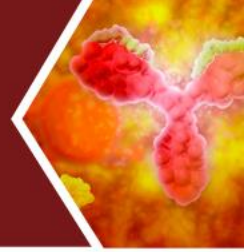


Summary Statements -

- SS#5: Assessment of T cell independent responses should generally wait until primary vaccine series is completed in children less than 18 mos
- SS#6: “Certain immunodeficiencies are drastic and pursuing evaluation of humoral immune function through vaccine antigen challenge would delay necessary therapy”
  - Severe combined immunodeficiency
  - Patients with combined immune deficiency
- SS#7: “Use of polysaccharide vaccines as a diagnostic tool must integrate numerous criteria”
  - Complex and evolving

Orange JS, et al. *J Allergy Clin Immunol*. 2012;130:S1-S24.

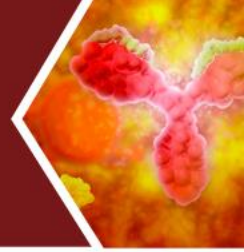
Immunologic Characteristics of Major Diagnostically Applied Vaccines



Vaccine	T-cell independent or dependent	Peak antibody levels	Protective levels
HIB conjugate	Dependent	6 mo (3-4 wk after third dose)	1.0 µg/mL
Meningococcal conjugate	Dependent	2-4 wk	2 µg/mL
Meningococcal polysaccharide	Independent	2-4 wk	2 µg/mL
Pneumococcal conjugate	Dependent	4 wk	≥1.3 µg/mL
Pneumococcal polysaccharide	Independent	4 wk	≥1.3 µg/mL
Rabies	Dependent	21 d after third dose for pre-exposure prophylaxis	0.5 IU
Tetanus	Dependent	2-3 wk after initial series	0.15 IU/mL

Orange JS, et al. *J Allergy Clin Immunol*. 2012;130:S1-S24.

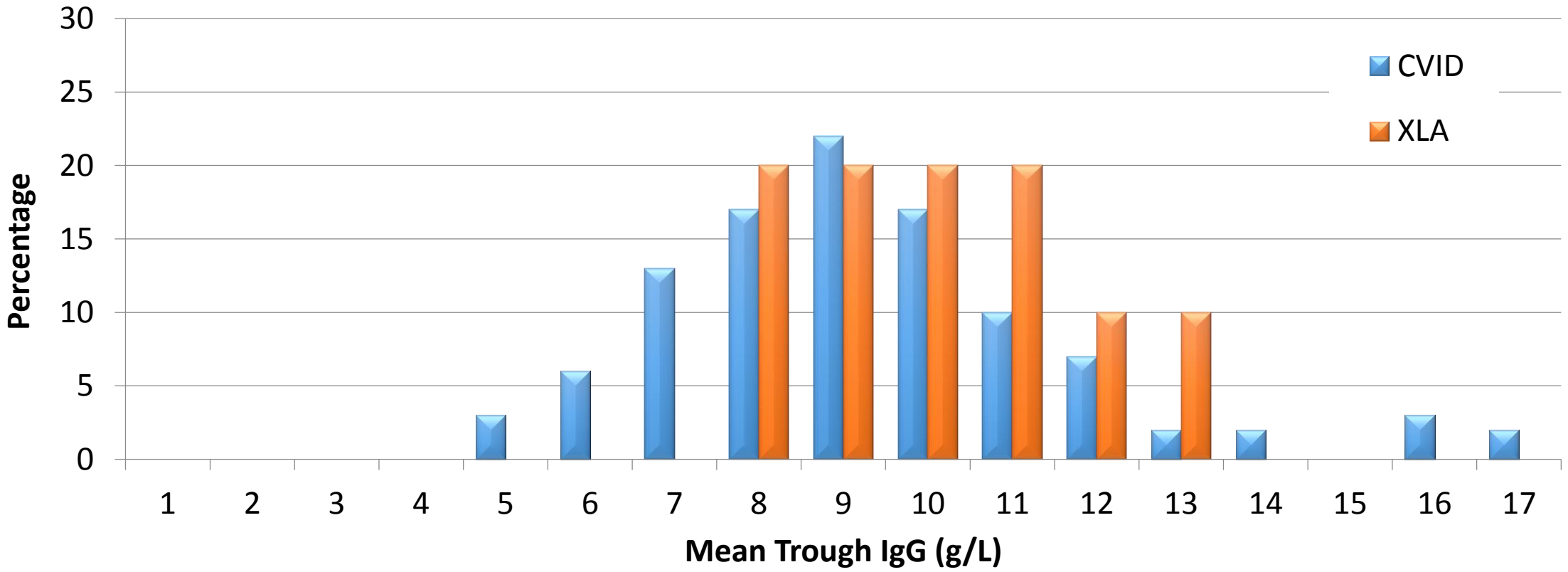
Ig Dose Varies According to Patient-specific Characteristics



- Dose by the intravenous (IVIG) route generally starts at 400-600 mg/kg/month and 100-175 mg/kg/week by the subcutaneous (SCIG) route
- Some patients require higher doses, especially those with chronic lung disease
- Recent studies have shown that an optimal trough level (for IVIG) or steady state IgG plasma level (for SCIG) is approximately 850 mg/dL to insure adequate infection prophylaxis

Bonilla FA, et al. *Ann Allergy Asthma Immunol*. 2005;94:S1-S63.

Prospective Analysis Over 22 Years: Mean Trough Levels that Kept Patients Infection-Free

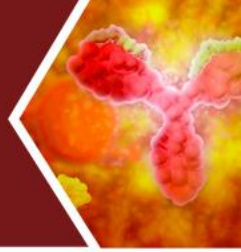


Infection score of <2.5 per year

XLA=X-linked agammaglobulinemia

Adapted from Lucas et al. *J Allergy Clin Immunology*. 2010:125(6):1354-1360.

Choice of Therapy and Dosing Should Be Guideline Based and Individually Tailored to the Patient

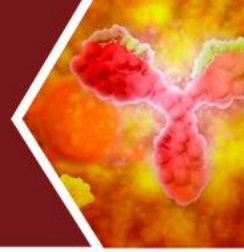


- Treatment course should follow the standards of care practice parameters from the American Academy of Allergy, Asthma and Immunology (AAAAI)
- According to the unpublished 2012 AAAAI “Physician Experiences with Insurance and Ig Therapy” survey of immunologists, the distribution of Ig delivery methods among the respondents was 57% IVIG and 42% SCIG

Bonilla FA, et al. *Ann Allergy Asthma Immunol*. 2005;94:S1-S63.

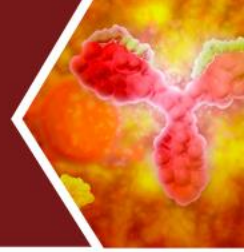
AAAAI. “Physician Experiences with Insurance and Ig Therapy.” Survey of AAAAI Immunologists. 2012.

Route of Ig Administration



- Route of administration of Ig therapy (ie, IVIG or SCIG) should be a decision based on discussions between the patient and provider
- The decision is typically based on any number of factors:
  - Clinical characteristics
  - Patient preference
  - Appropriate site of care (ie, home, hospital, infusion center)
  - Insurance coverage

IVIG Administration



Advantages

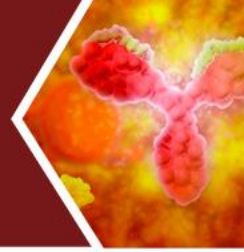
- Data on clinical use for over 30 years
- Ability to give large volumes per infusion allows intermittent dosing (every 21–28 days)

Disadvantages

- Requires venous access and trained personnel in most situations
- Large shift in IgG levels during dosing may cause adverse effects at or just after peak and during low troughs
- Home infusion is possible, but more technically demanding than subcutaneous (SC) administration

Berger M. *Clin Immunol*. 2004;112:1-7.

SCIG Administration



Advantages

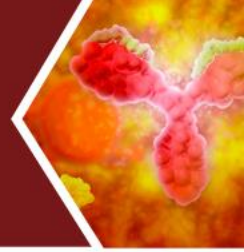
- Data on clinical use for over 20 years internationally
- Facilitates self- or home-infusion
- Venous access not required
- Gradual absorption maintains more consistent IgG levels
- New delivery method of facilitated SCIG administration

Disadvantages

- Requires frequent dosing due to relatively small volume per infusion
- Ability to self-infuse requires reliable and adherent patient
- Multiple infusion sites may be required

Berger M. *Clin Immunol*. 2004;112:1-7.

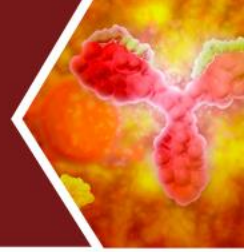
Ig Products are *NOT* Generic and/or Interchangeable



Intravenous	Subcutaneous	Both Intravenous and Subcutaneous
• Bivigam - Biotest Pharmaceuticals • Carimune ® NF, Nanofiltered - CSL Behring • Flebogamma DIF 5% - Instituto Grifols • Flebogamma DIF 10% - Instituto Grifols • GamaSTAN® S/D, Immune Globulin (Human) - Grifols Therapeutics • Gammagard Liquid - Baxalta • Gammagard S/D - Baxalta • Gammaplex - Bio Products Laboratory • Gamunex-C - Grifols Therapeutics • OCTAGAM - OCTAPHARMA • Privigen - CSL Behring	• Hizentra - CSL Behring • HYQVIA - Baxalta	• Gammagard Liquid - Baxalta • Gamunex-C - Grifols Therapeutics

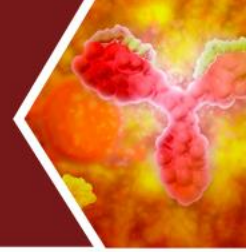
FDA. Immune Globulins.
http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm127589.htm

Barriers to Optimizing Care: Coverage and Reimbursement



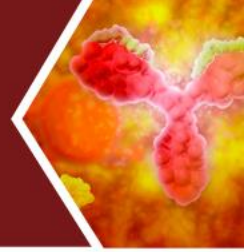
- The prior authorization processes implemented by many health plans create barriers to Ig product coverage and physician reimbursement
- These barriers are exacerbated by specific factors associated with the treatment of PI with Ig replacement therapy:
  - Inadequate ICD-9 codes
    - New ICD-10 codes much more comprehensive
  - Inadequate information from the physician in claims submission
    - The omission of immunization responses to vaccines during the diagnostic process may delay approval
  - Inadequate or outdated medical records for patients on Ig replacement therapy for many years
    - This has the potential to compromise patient care if a patient has to discontinue therapy due to coverage issues

Barriers to Optimizing Care: Dosing and Product Selection



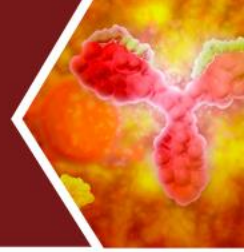
- The nuances of Ig replacement therapy may result in barriers related to appropriate and adequate dosing
  - Specialty pharmacists may dictate dosing without a full appreciation of the clinical course of the patient
  - An apparent fixation on trough levels of 500 mg/dL has the potential to limit the appropriate dosing of patients

Barriers to Optimizing Care: Dosing and Product Selection (cont.)



- Product selection is paramount, since Ig products are not generic and/or interchangeable
  - Switching products after tolerability has been demonstrated with a given product can result in adverse events and reduced efficacy
  - Formulary restrictions may mandate selection of a 5% IVIG product over a 10% IVIG product regardless of clinical appropriateness

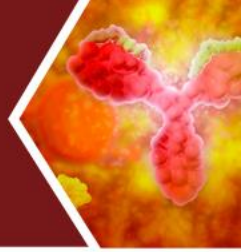
Barriers to Optimizing Care: Site of Care and Patient Considerations



- Beyond appropriate dosing and administration, patient satisfaction and resultant adherence are crucial for treatment success
- In a recent survey of individuals with PI, most respondents (76%) were satisfied with their current treatment
  - However, patients remained below the physical and mental well-being norms for health-related quality of life as determined by the questionnaire
  - All respondents expressed a desire for once monthly infusions, the ability to administer these at home, self-administration, shorter duration of administration, and fewer needle sticks

Espanol et al. *Patient Prefer Adherence*. 2014; 8: 621–629

Barriers to Optimizing Care: Site of Care and Patient Considerations (cont.)

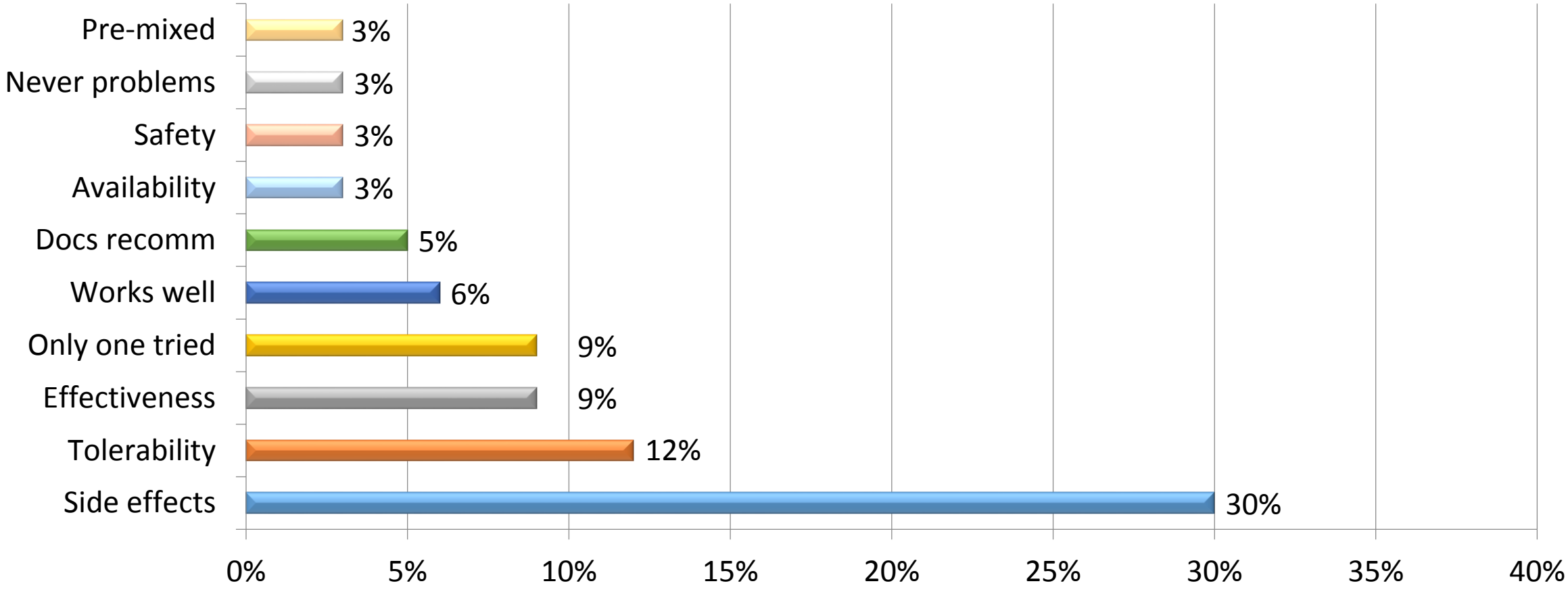


Patient choice in route of administration has been shown to be a viable means of promoting treatment satisfaction and adherence

SCIG is generally preferred due to matters of convenience related to self-administration, poor venous access, adverse events

IVIG is generally preferred due to difficulties self-administering SCIG, pain from multiple injections, and associated adherence issues

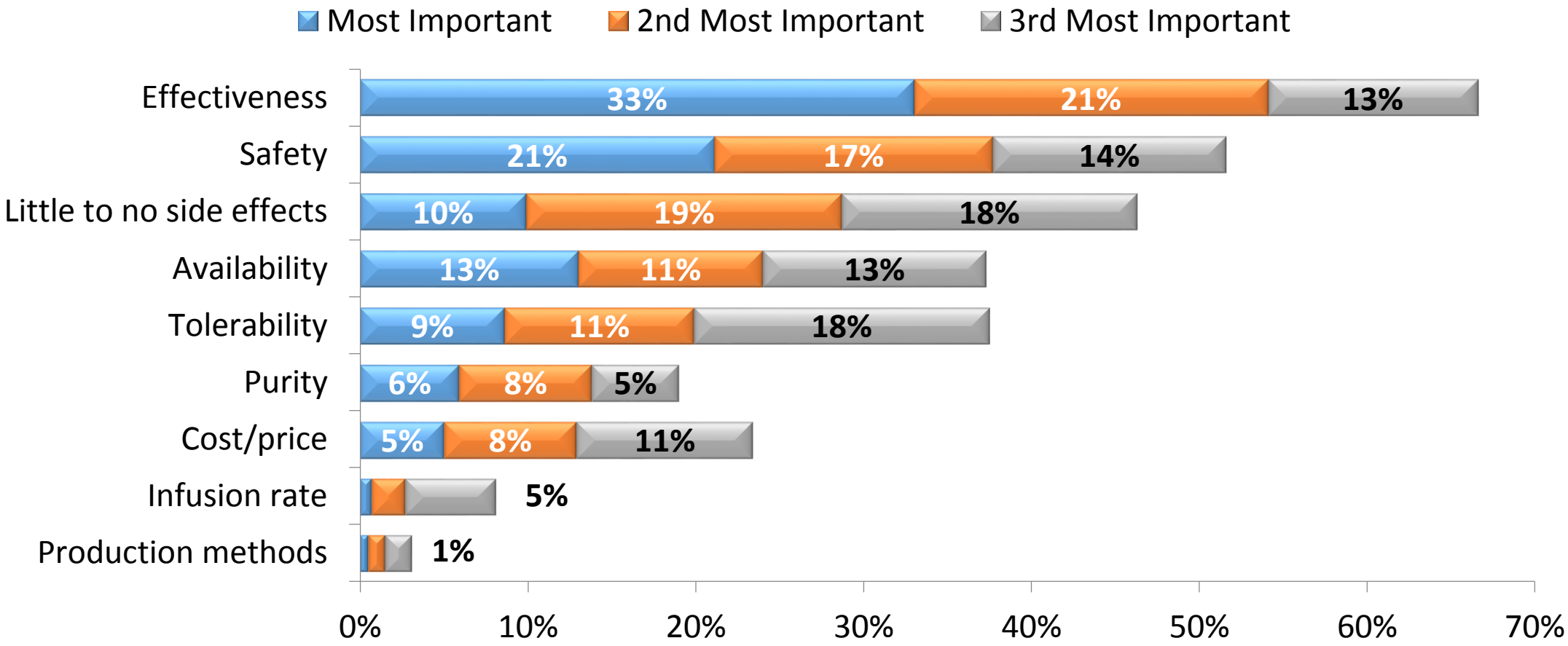
Why Patients Prefer Specific Products



Q54c. Why do you prefer that/those product(s)? N=692

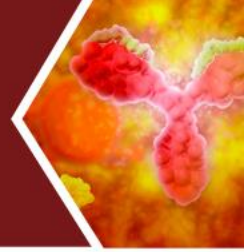
IDF Treatment Survey: 2003

Most Important Properties of IgG Therapy Ranked According to Importance

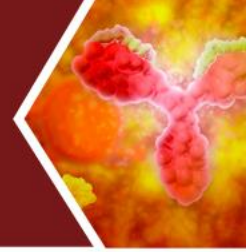


Q23. What are the THREE most important things when considering an IgG therapy product?
Base: Those reporting current IgG Therapy use., N= 882, multiple selection

Summary/Closing



- Not all infections can be prevented, but the goal of antibody replacement therapy is that the frequency and severity of infections will be significantly decreased so that permanent organ damage can be avoided
- A tailored regimen must be developed for each patient and modified as necessary to achieve the treatment goals and meet the needs of unique individuals
- After a diagnosis of PI has been made, therapy is most often life-long, with the exception of rare instances in which reevaluation of the diagnosis is performed by taking the patient off of therapy and reevaluating humoral immunity



“…the greatest teachers of modern immunology: patients with immunodeficiency diseases.”

Robert A. Good, MD, DSc, PhD

Effectiveness, Costs, and Results of Collaborative Care Approaches to Optimize Outcomes in

Antibody Replacement Therapy

Jointly provided by

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MEDICAL EDUCATION RESOURCES

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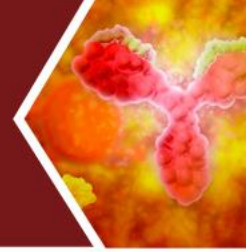
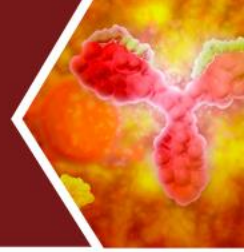


Pharmacoeconomic Assessment: Considerations to Evaluate the Total Cost of Care

Alan Lyles, ScD, MPH, RPh
Henry A. Rosenberg Professor of Government, Business, and Nonprofit Partnerships
Fellow, National Academy of Public Administration
University of Baltimore

Faculty Disclosure

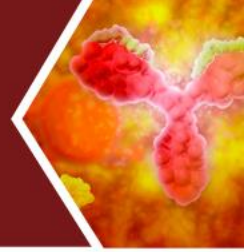


- The ***faculty*** reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:

  Alan Lyles, ScD, MPH, RPh

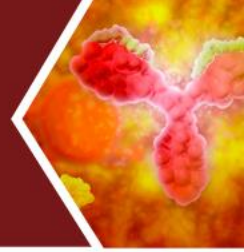
  - No financial interest/relationship relating to the topic of this activity

Overview



- Total cost of care for a given condition =
  - (Treatment costs + medical expenditures associated with disease-related morbidity and mortality)
- Pharmacoeconomic assessments are developed from the total cost of care for accuracy, completeness, and to provide practical guidance
- Comprehensive analyses weigh costs averted by medical intervention against the costs of the intervention itself to determine if these latter costs are offset by savings
  - Immunoglobulin (Ig) replacement therapy, a lifelong and lifesaving treatment for primary immunodeficiency (PI), demonstrates such offset costs among medical interventions

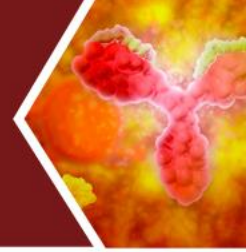
Economic (& Clinical) Studies: Pharmaceutical Value vs Affordability



	CEA	BIM
Value (Societal)	✔	
Budget Realities		✔
Academic Publications	✔	
Impact		
Citation	✔	
Typical time horizon		
Long(er) term	✔	
Budget cycle		✔

CEA=comparative effectiveness analyses; BIM=budget impact model

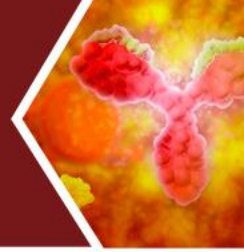
Knowledge



"Men [sic] more frequently require to be reminded than informed."

Samuel Johnson: Rambler #2 (March 24, 1750)

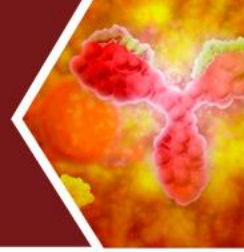
Reasons Clinicians Depart from Practice Guidelines



- Barriers to Physician Adherence
  - Lack of awareness
  - Lack of familiarity
  - Lack of agreement
  - Lack of self-efficacy
  - Lack of outcome expectancy
  - Inertia of previous practice
- Guideline Related Barriers
- Patient Related Barriers
- Environmental Related Barriers

Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud P-A C and Rubin HR. Why Don't Clinicians Follow Clinical Practice Guidelines? A Framework for Improvement. *JAMA* 1999;282(15):1458-1465.

Underutilization of Recommended Services: How Effective Can Pharmaceuticals Be in Usual Community Practice?

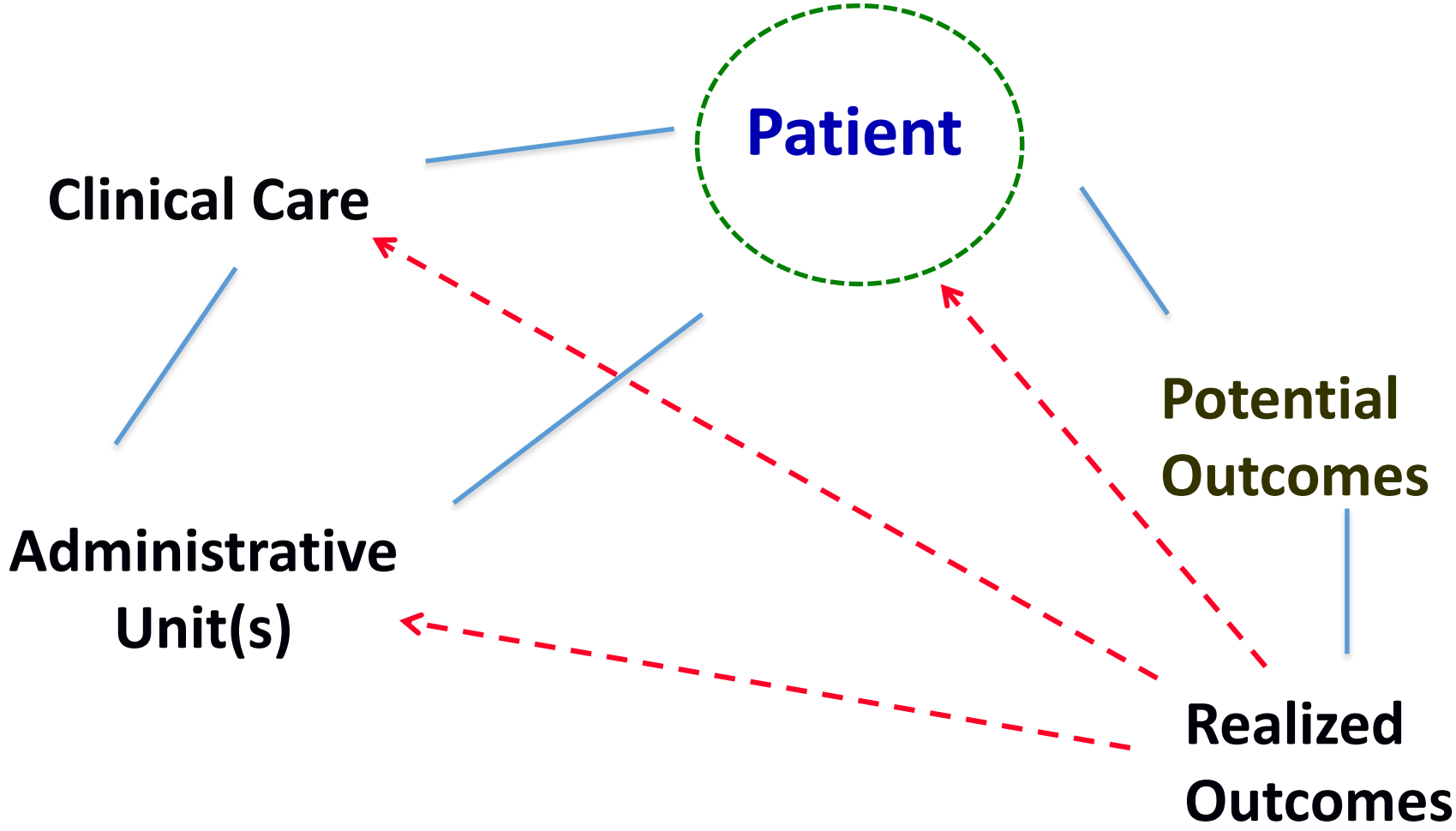


Adherence to Quality Indicators, Overall and According to Type of Care and Function

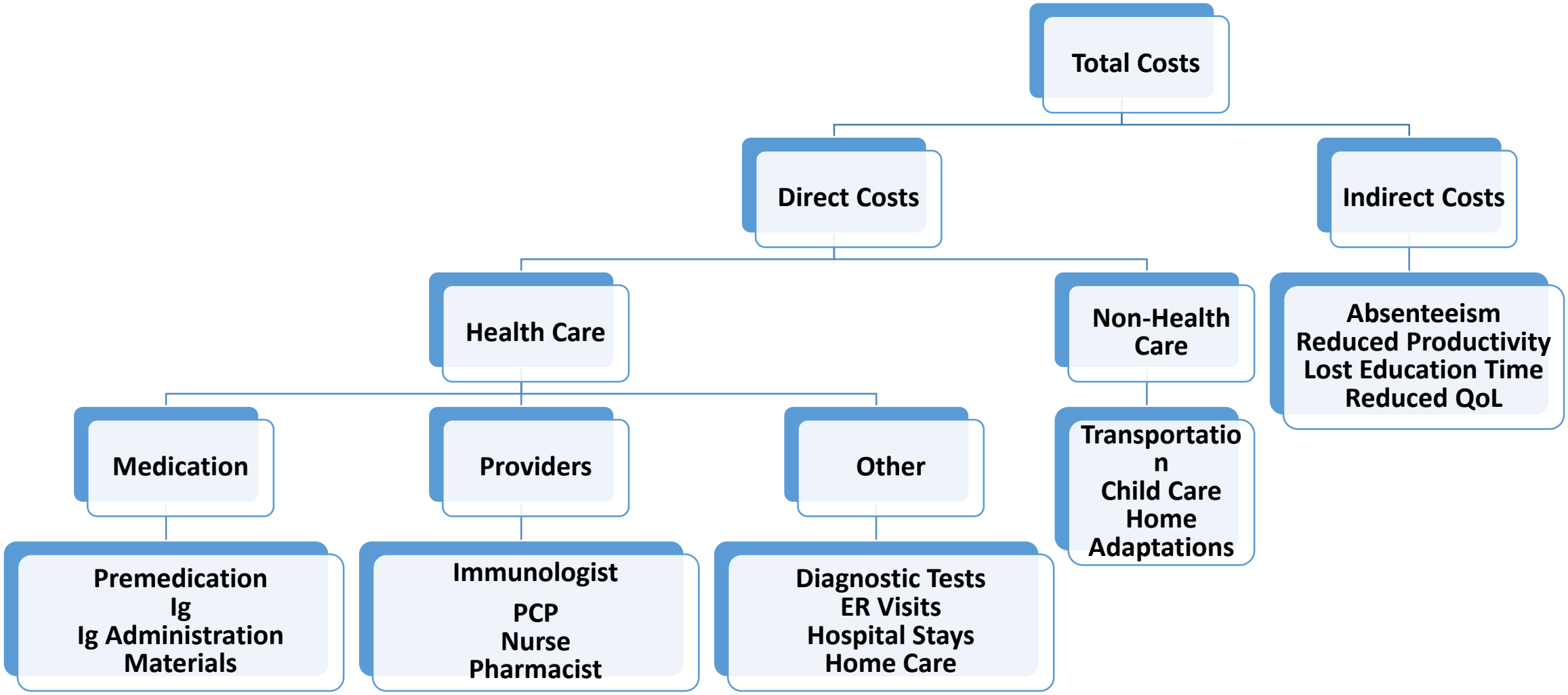
Variable	No. of Indicators	No. of Participants Eligible	Total No. of Times Indicator Eligibility Was Met	Percentage of Recommended Care Received (95% CI)
Overall care	439	6712	98,649	54.9 (54.3-55.5)
Type of care				
Preventive	38	6,711	55,268	54.9 (54.2-55.6)
Acute	153	2,318	19,815	53.5 (52.0-55.0)
Chronic	248	3,387	23,566	56.1 (55.0-57.3)
Function				
Screening	41	6,711	39,486	52.2 (51.3-53.2)
Diagnosis	178	6,217	29,679	55.7 (54.5-56.8)
Treatment	173	6,707	23,019	57.5 (56.5-58.4)
Follow-up	47	2,413	6,465	58.5 (56.6-60.4)

McGlynn E, Asch AM, Adams J, et al. The Quality of Health Care Delivered to Adults in the United States. *NEJM.* 2003;348:2536-2645.

Potential Outcomes = Values Not Value
An Rx-Centric, Systems Perspective

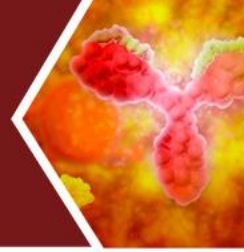


The Direct and Indirect Costs of PI: Diverse and Complex



Simoens S. *Exp Rev Pharmacoeconomics Outcomes Res*. 2009;9:375-386.

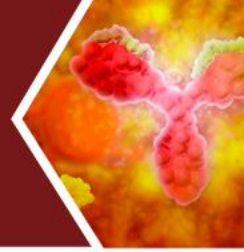
Total Cost of Care for Primary Immunodeficiency (PI)



- **Total cost of care** = drug costs (primarily Ig replacement therapy) + costs associated with unmanaged or inadequately managed disease (ie, the costs associated with serious infections: ED utilization, hospitalizations, antibiotics, antivirals, etc)
- According to a 2015 analysis, the total estimated cost of diagnosed **common variable immunodeficiency (CVID)** is $274,200/patient annually
- Hospital admission cost ($25,000/patient) accounts for the most important expenditure parameter before diagnosis

Sadeghi et al. *Exp Rev Clin Immunol*. 2015;11:681-688.

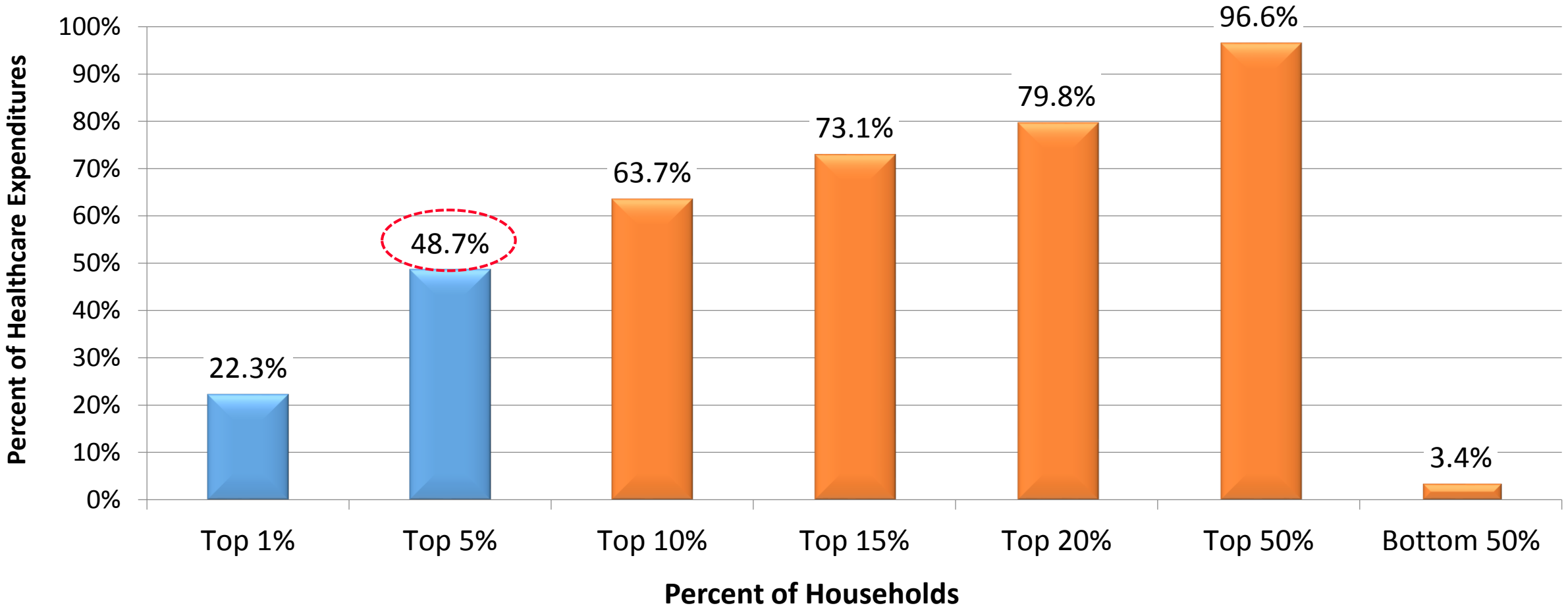
Primary Immunodeficiency (PI) Drug Costs



- **Ig**, the only treatment for PI, as with other specialty drugs, has a relatively high acquisition cost compared with traditional pharmaceutical products
- Medicare reimbursement for the cost of an Ig product is ~$33,000 per year per patient
- In a 2015 analysis, medication cost ($40,600/patient) was the main cost factor of CVID after diagnosis, primarily due to monthly administration of immunoglobulin (included drug acquisition cost and administration costs/hospital charges)
  - *Despite the high cost of Ig replacement therapy, this component accounted for <15% of the total cost of care in CVID*

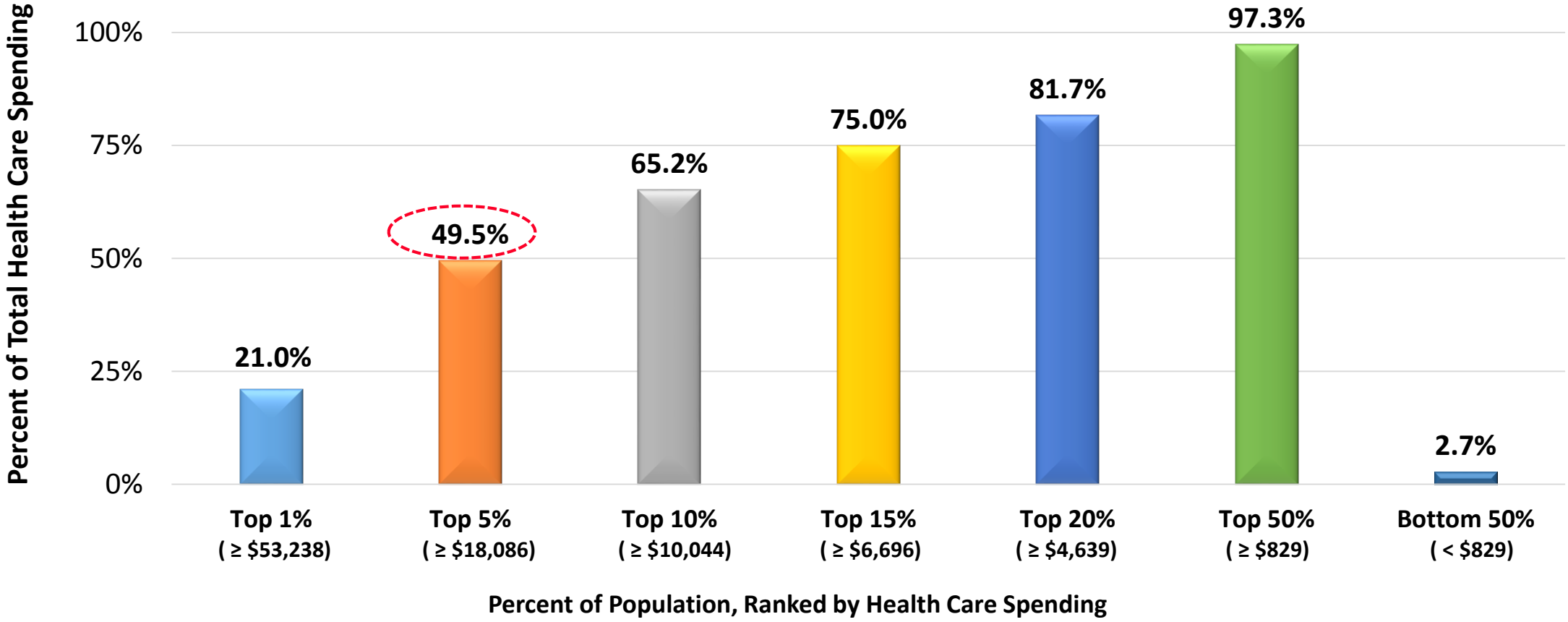
CMS. 2015 ASP Drug Pricing Files. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B Drugs/McrPartBDrugAvgSalesPrice/2015ASPFiles.html
Sadeghi et al. *Exp Rev Clin Immunol*. 2015;11:681-688.

Concentration of Health Spending in the Total U.S. and Family Populations, 2002



Kaiser Family Foundation. Trends and Indicators, 2005 Update, Exhibit 1.11.

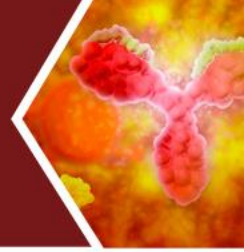
Concentration of Health Care Spending in the U.S. Population, 2010



NOTE: Dollar amounts in parentheses are the annual expenses per person in each percentile. Population is the civilian noninstitutionalized population, including those without any health care spending. Health care spending is total payments from all sources (including direct payments from individuals and families, private insurance, Medicare, Medicaid, and miscellaneous other sources) to hospitals, physicians, other providers (including dental care), and pharmacies; health insurance premiums are not included.

Kaiser Family Foundation calculations using data from U.S. Department of Health and Human Services, Agency for Healthcare Research and Quality, Medical Expenditure Panel Survey (MEPS), Household Component, 2010.

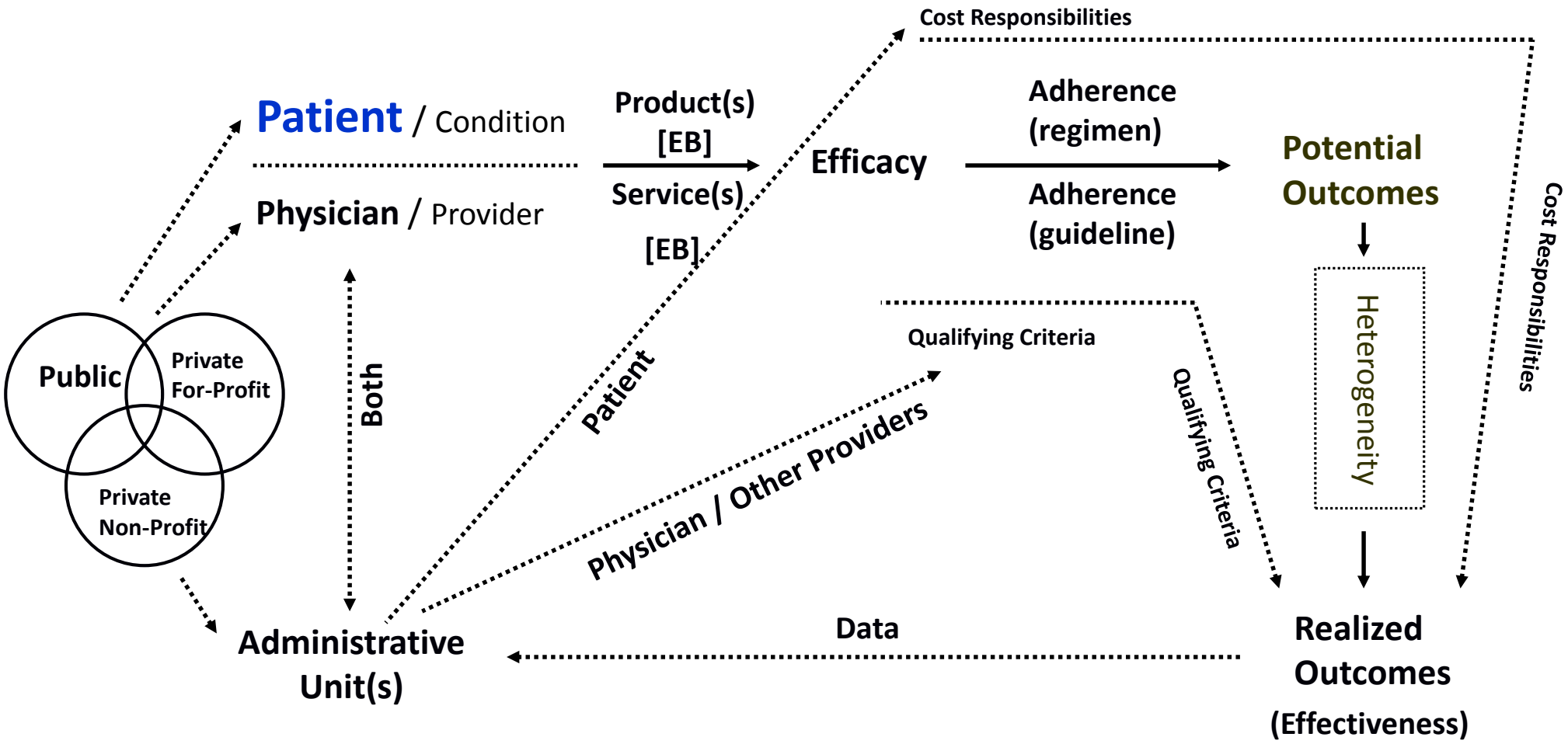
Costs Averted Through Management/Treatment of PI



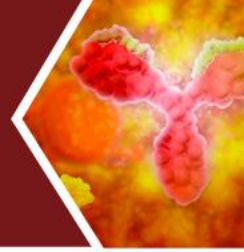
- Due to the morbidity and mortality associated with PI, failing to treat patients or undertreating patients with antibody deficiencies ultimately carries an even higher total cost of care
- In a 2015 analysis (Sadeghi, et al.), early diagnosis of CVID was estimated to save $6,500/patient/year in (2010 US$)
- A 2011 study estimated the cost of non-treatment to be $138,760
  - In terms of indirect costs, treating these disorders with Ig saves $78,166 per patient/per year and prevents 25 missed days of work/year

Sadeghi et al. *Exp Rev Clin Immunol*. 2015;11:681-688.
Modell et al. *Immun Res*. 2011;51:61-70

Actual Versus Potential Outcomes from a Systems Perspective



Delivery System Choices Influence Realized Outcomes for Patients with PI



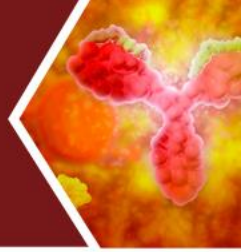
Narrow or ultra-narrow networks create barriers in access to appropriate specialists such as **immunologists**

About Highmark's offerings for next year, he said, "Is there going to be a trend toward more narrow networks? Yes."

- David L. Holmberg, CEO, Highmark

Mathews AW. *Wall Street Journal*. September 3, 2015. Available at: http://www.wsj.com/articles/highmark-is-latest-to-trim-offerings-under-health-law-1441324514.

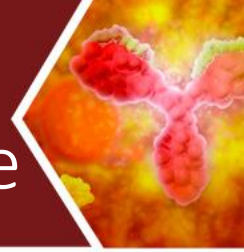
The Pharmacoeconomic Implications of Appropriate Therapy Are Substantial



- Appropriate treatment includes Ig replacement therapy and access to immunologists
- The total cost of clinically appropriate Ig replacement therapy has offsets from averted morbidity and mortality in patients with untreated PI
- Data on the cost of under-treating PI are not currently available
  - However, given the high cost of treating serious infections such as pneumonia, an Immune Deficiency Foundation (IDF) Task Force concluded that insufficient treatment is not advisable from clinical, cost, quality of life (QoL), or productivity perspectives

Baldzicki M, et al. for the Immune Deficiency Foundation. Primary Immunodeficiencies: Optimal Policies and Practices. October 2013.

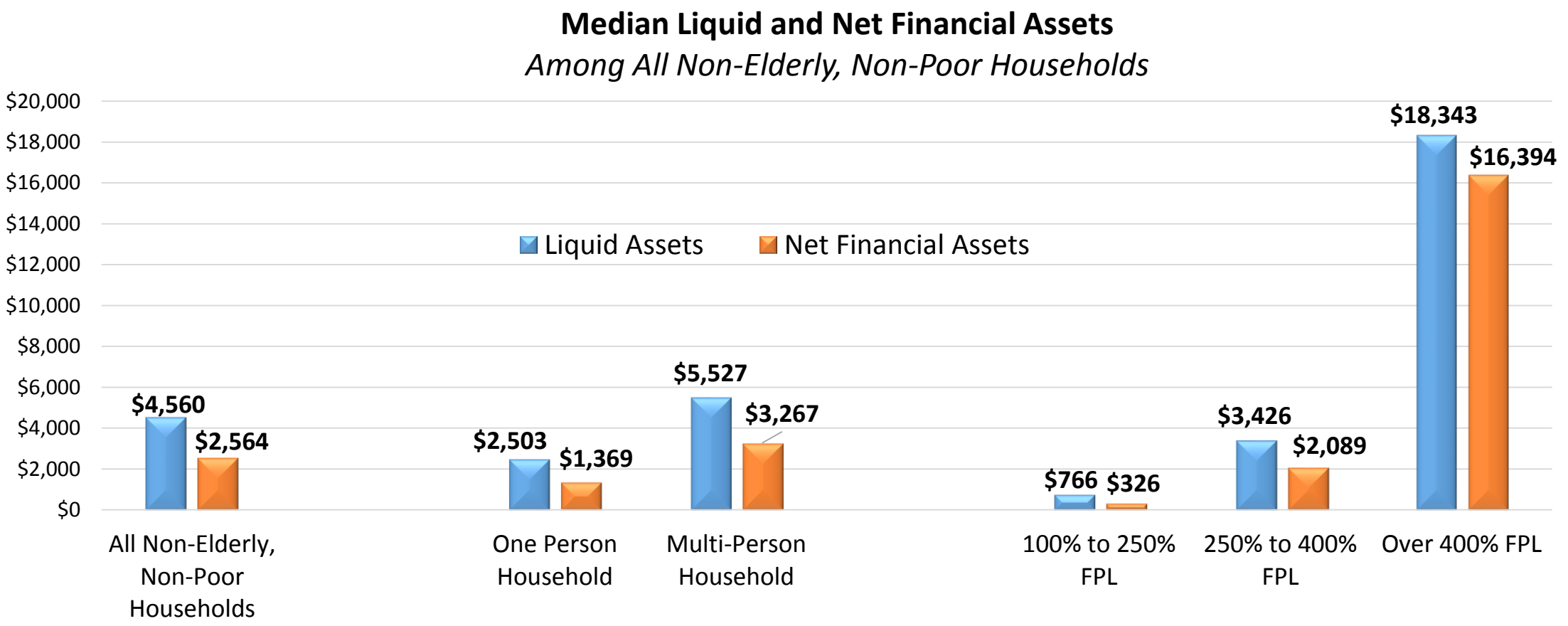
Appropriate & Timely Treatment is Paramount to Pharmacoeconomic Outcomes Regardless of Ig Administration Route



- Drug acquisition costs for IVIG and SCIG are comparable, and both have a distinct place in therapy given the diverse population of patients with PI
- A 2013 meta-analysis reported:
  - SCIG was considerably more cost-effective than IVIG due to missed work and school days associated with the administration of IVIG
  - Both routes of administration were clinically effective in terms of infection prophylaxis

Lingman-Framme et al. *Drugs*. 2013;73:1307-1319.

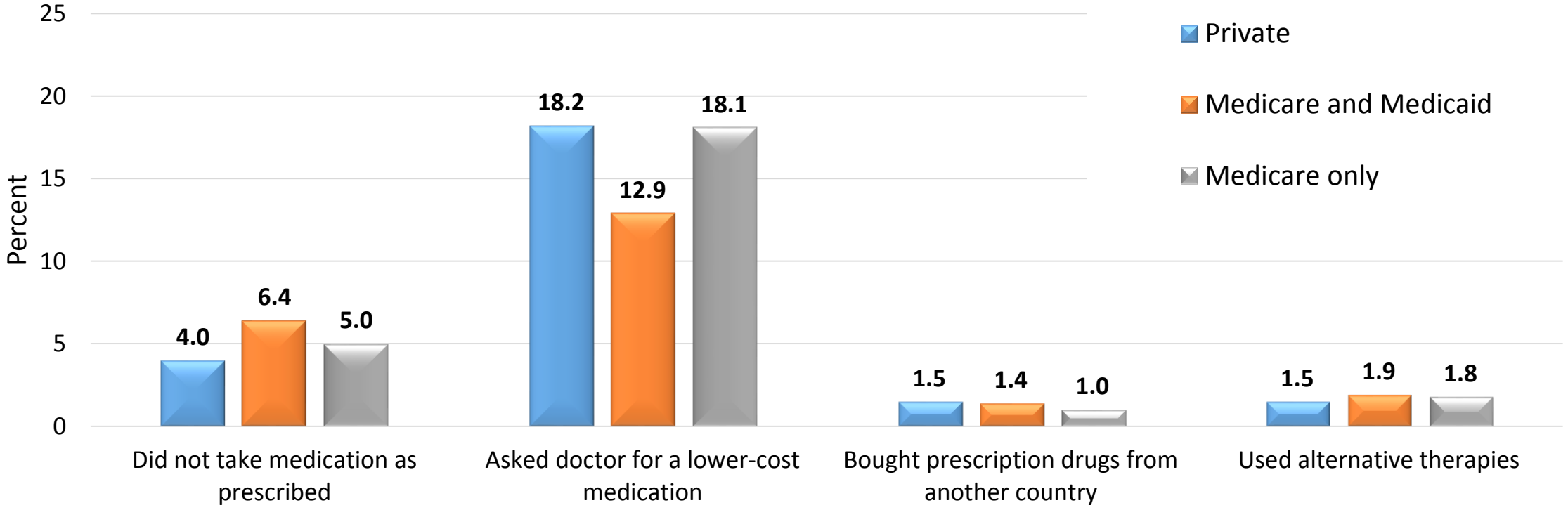
Benefit Design & Cost-sharing Requirements Influence Effective Demand



NOTES: FPL refers to the 2013 Federal Poverty Level.
SOURCE: Kaiser Family Foundation analysis of 2013 Survey of Consumer Finance (SCF) data.

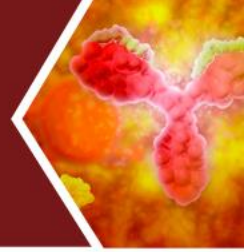
Claxton G, Rae M and Panchal N. Issue Brief: Consumer Assets and Patient Cost Sharing. Kaiser Family Foundation. February 2015. http://files.kff.org/attachment/issue-brief-consumer-assets-and-patient-cost-sharing

Benefit Design Consequences: Strategies Used by Adults to Reduce Their Prescription Drug Costs: United States, 2013



Cohen RA, et al. *NCHS Data Brief*. 2015;184:1-8. http://www.cdc.gov/nchs/data/databriefs/db184.pdf

Summary



- The product cost of Ig replacement therapy for PI is a key component of the total cost of care, however, total costs associated with unmanaged or under-managed disease are substantially higher
- The AAAAI practice parameter should serve as a guideline for appropriate, adequate care, but one size does not fit all for patients with PI
- PI patients' total costs of care are typically reduced after diagnosis due to appropriate management with Ig replacement therapy

Effectiveness, Costs, and Results of Collaborative Care Approaches to Optimize Outcomes in

Antibody Replacement Therapy

Jointly provided by

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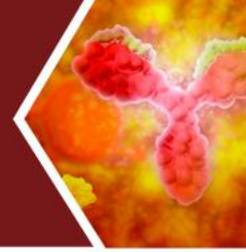
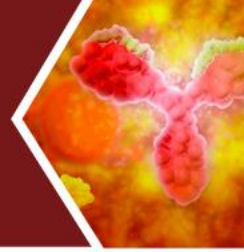


Managed Care Approaches for Providing Cost-effective Therapy and Improving Patient Outcomes

Jeffrey Dunn, PharmD, MBA
Chief Clinical Officer
Senior Vice President
VRx Pharmacy Services, LLC

Faculty Disclosure



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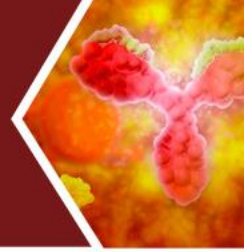
  Jeffrey Dunn, PharmD, MBA

  - *Consulting Fees:* Amgen Inc., Biogen, Janssen Pharmaceuticals, Inc., Pfizer Inc.

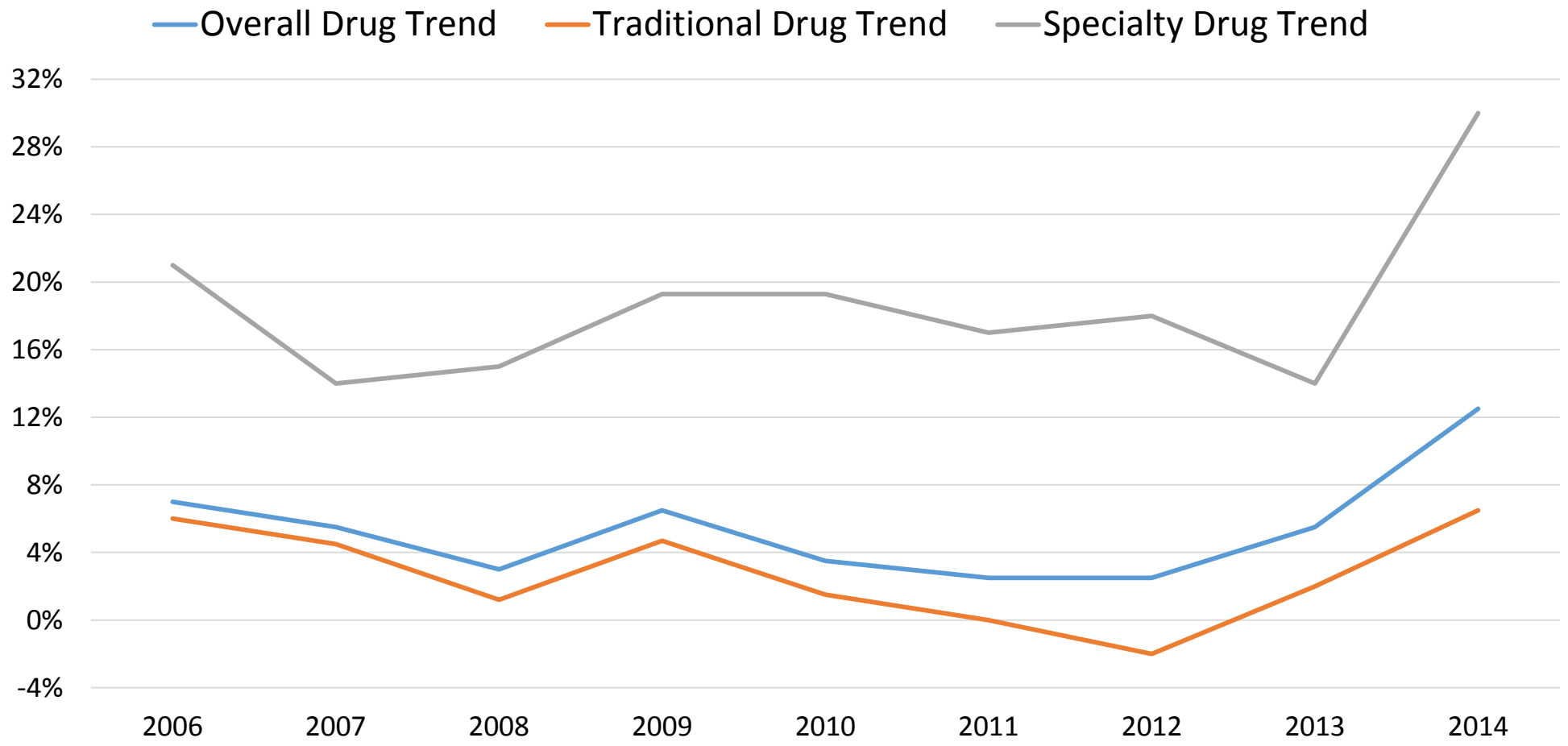
Specialty Drugs Constitute the Fastest Growing Segment of the Drug Trend



- While the traditional pharmaceutical trend has remained relatively flat, specialty drug spending has increased consistently over the past several years
    - Prescription drug spending increased 13.1% in 2014, largely driven by an unprecedented 30.9% increase in spending on specialty medications
    - Utilization of traditional medications stayed flat (-0.1%), while the use of specialty drugs increased 5.8%
    - Price increases for these medication categories – 6.5% for traditional and 25.2% for specialty—were contributing factors
- Specialty medications represent only 1% of all U.S. prescriptions, these medications represented 31.8% of all 2014 drug spend: an increase from 27.7% in 2013

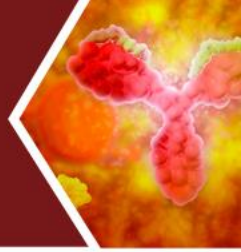
Express Scripts. Drug Trend Report. 2014. http://lab.express-scripts.com/drug-trend-report/

Traditional, Specialty, and Overall Drug Trend 2006-2014



Express Scripts. Drug Trend Report. 2014. http://lab.express-scripts.com/drug-trend-report/

The Broad "Immune Deficiency" Class Represents a Leading Specialty Category in Managed Care

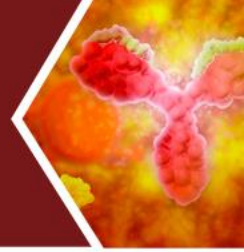


		TREND		
RANK	**THERAPY CLASS**	**MEDICARE**	**COMMERCIAL**	**DIFFERENCE**
1	Hepatitis C	1,067.5%	742.6%	324.9%
2	Miscellaneous Specialty Conditions	56.6%	35.6%	21.0%
3	Oncology	37.2%	20.7%	16.5%
4	Inflammatory Conditions	30.7%	24.3%	6.4%
5	Multiple Sclerosis	27.9%	12.9%	15.0%
6	Pulmonary Arterial Hypertension	24.0%	13.8%	10.2%
7	***Immune Deficiency****	***23.6%***	***21.2%***	***2.4%***
8	Blood Cell Deficiency	9.6%	0.9%	8.7%
9	HIV	8.3%	14.8%	-6.5%
10	Anticoagulants	-15.9%	-14.1%	-1.8%
	TOTAL SPECIALTY	**45.9%**	**30.9%**	**15.0%**

Includes autoimmune deficiency and acquired immune deficiency in addition to PI

Express Scripts. Drug Trend Report. 2014. http://lab.express-scripts.com/drug-trend-report/

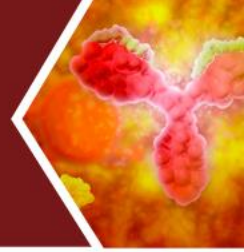
Immune Deficiency Trails Only Hepatitis C and Inflammatory Conditions in the Commercial Trend



- The immune deficiency class was growing at a rate of 21.2% among commercial lines of business as of 2014, trending ahead of even oncology at 20.7%
- PI, where Ig replacement represents the only viable pharmacologic treatment, is not the driving factor behind this growth
  - Instead, increased utilization in other areas, including off-label uses and neurological indications, are the key drivers

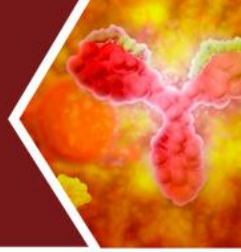
Express Scripts. Drug Trend Report. 2014. http://lab.express-scripts.com/drug-trend-report/

PI is Only One of >40 Disease Categories that Use Ig and One of Six FDA-approved Uses of Ig



- Other approved uses include chronic inflammatory demyelinating polyneuropathy, idiopathic thrombocytopenic purpura, Kawaski disease, chronic B-cell lymphocytic leukemia, and multifocal motor neuropathy
- Upwards of 100 off-label uses for Ig include multiple sclerosis, graft-versus-host disease in transplant recipients, prevention of antiphospholipid syndrome in miscarriage, and Guillain-Barré syndrome

Ig Replacement is Lifesaving, Lifelong Treatment for PI but Only Represents a Third of Overall Ig Use

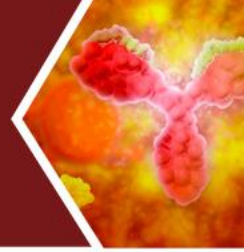


IVIG & Subcutaneous Immune Globulin – United States *United States IVIG Forecast, 2009 – 2015*		
	Percentage of Usage Volume	Patients Growth Per Year
Primary Immunodeficiencies	36.0%	2.1%
Neurology	25.1%	9.9%
Hematology / Oncology	25.7%	3.8%
Cardiology	1.5%	5.6%
Rheumatology / Nephrology	5.4%	11.5%
All Others*	6.3%	13.4%
TOTAL	**100.0%**	**8.2%**

*Dermatology, Infectious diseases, Ophthalmology, Obstetrics/Gynecology, others

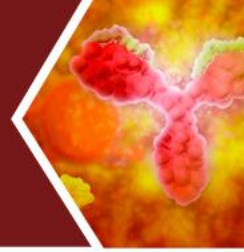
Immune Deficiency Foundation. Research findings. 2013

A Multitude of Indicated and Off-label Uses for Ig Has Drawn Increased Attention from Payer Stakeholders



- Specialty drugs had already become an area of increased focus for payer management efforts, due to the high cost and increased utilization trend
- Ig therapies, which carry a high potential for inappropriate and/or off-label use, are one area receiving enhanced attention in terms of management interventions
- In PI, where Ig replacement therapy serves as a lifelong, lifesaving therapy and further represents the only available pharmacologic treatment modality, these management efforts must be carefully tempered

Current Utilization Management Tools by Class



	CARE MANAGE-MENT*	PRIOR AUTHORIZA-TION	STEP EDIT REQUIREMENTS	CLINICAL PATHWAYS	POST-SERVICE CLAIM EDITS	OTHER	NONE
Autoimmune Disorders	24%	98%	39%	10%	22%	5%	0%
Cancer	32%	85%	20%	27%	22%	5%	5%
Immunodeficiencies	**24%**	**80%**	**15%**	**2%**	**22%**	**2%**	**5%**
Multiple Sclerosis	20%	88%	34%	7%	20%	5%	2%
Osteoporosis	7%	80%	32%	2%	20%	5%	5%
Osteoarthritis	5%	59%	22%	2%	22%	7%	17%
Age-Related (Wet) Macular Degeneration	2%	68%	15%	2%	20%	5%	20%

n=41 payers, 120 million covered lives

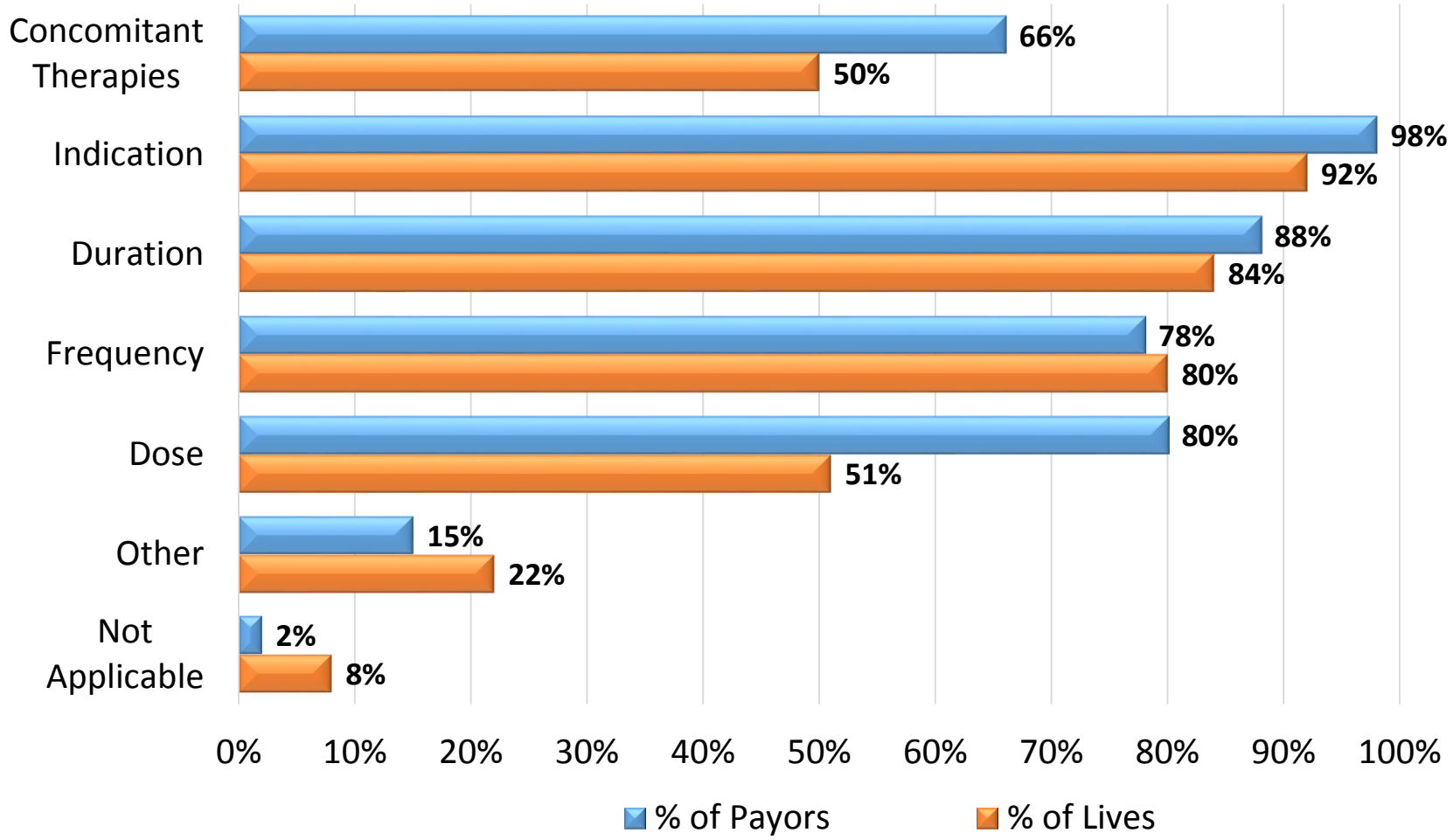
*(eg, disease management or case management)

Magellan Pharmacy Solutions. Medical Pharmacy & Oncology Trend Report 2014.

Prior Authorization Remains the Most Common Intervention for Managing Therapies for PI

Medical Benefit Drug Prior Authorization Criteria

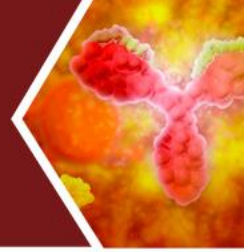
- Currently, FDA-labeled indication is the most common criterion across all classes of medications
- In Ig replacement therapy for PI, consideration may be given to incorporate dosing that ensures optimal trough levels and the highest likelihood for effective infection prophylaxis



n=41 payers, 120 million covered lives

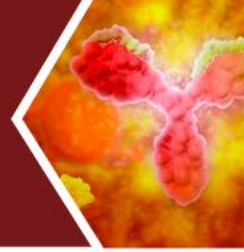
Magellan Pharmacy Solutions. Medical Pharmacy & Oncology Trend Report 2014.

Cost Sharing Considerations



- In the wake of reform legislation and tighter health care budgets, plans are increasingly shifting a greater proportion of costs to the member
- With copays as low as $30 demonstrating an adverse effect on adherence even in immediately life-threatening conditions such as cancer, payers must be ever aware of the impact of such measures

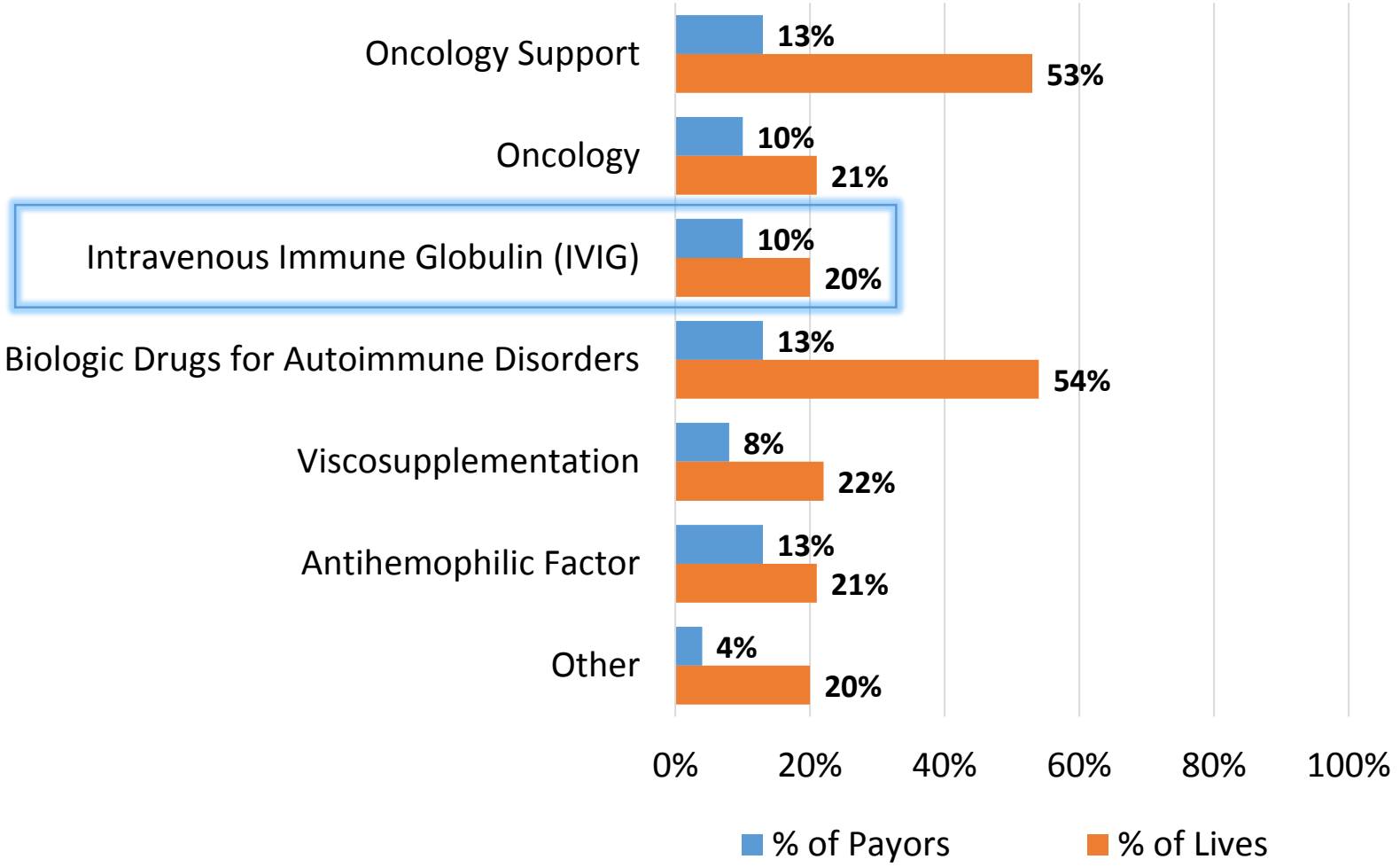
Site of Care/Channel Management Considerations



- Certain settings, namely those outside of hospitals/facilities, carry inherently lower costs in terms of drug administration
  - However, not all sites of care are appropriate for all patients: one size does not fit all
- Distribution channel management interventions that drive care to lower cost sites of care are value based in terms of costs to both the plan and member
  - Patients' individual clinical needs and preferences must be taken into consideration for the sake of promoting adherence
- Coordinating how medications are managed between medical and pharmacy benefits to increase and maintain patient compliance for specific diseases may also improve transparency, pricing, potential for contracting, adjudication, etc

Management Under the Pharmacy Benefit Also Allows for Carving Out to PBMs

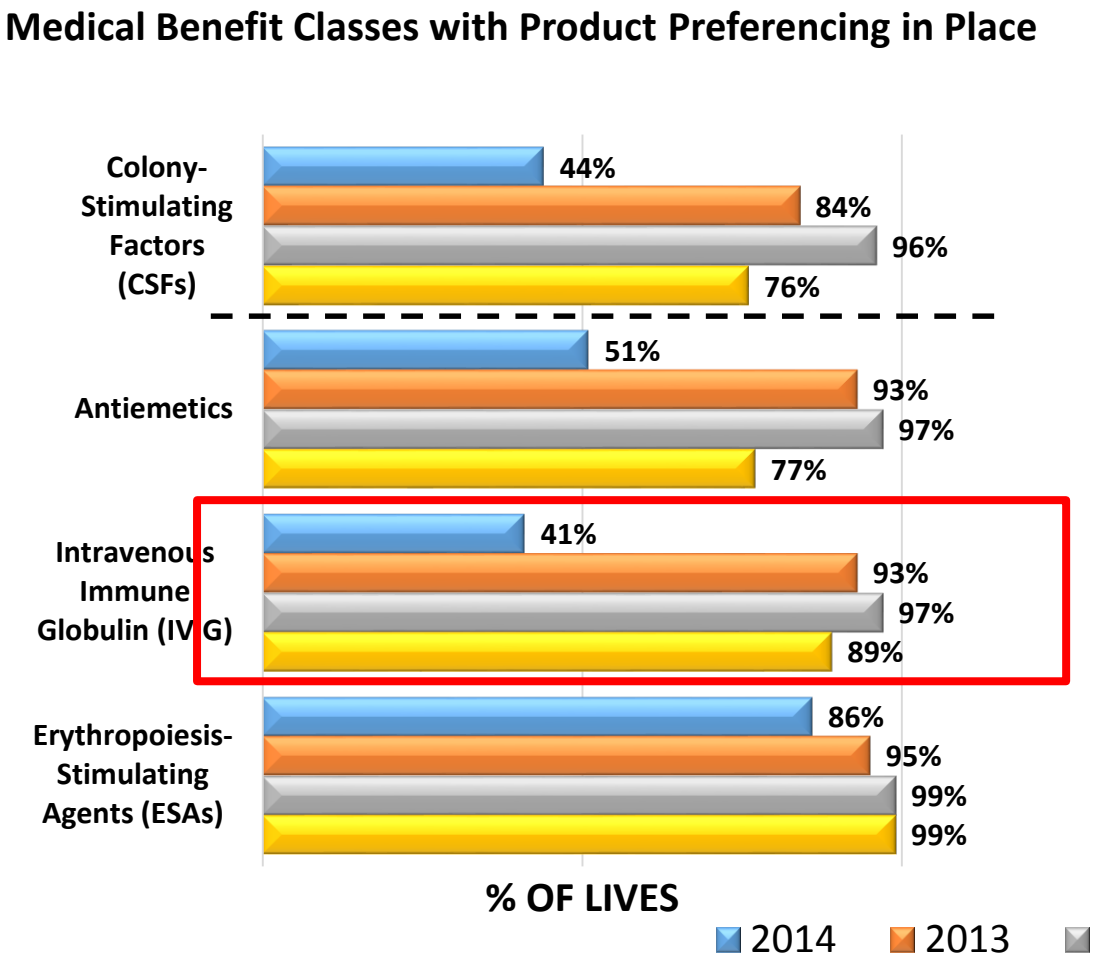
Therapeutic classes of medical benefit drugs self-insured clients were carving out to the pharmacy benefits manager (PBM) for management under the pharmacy benefit

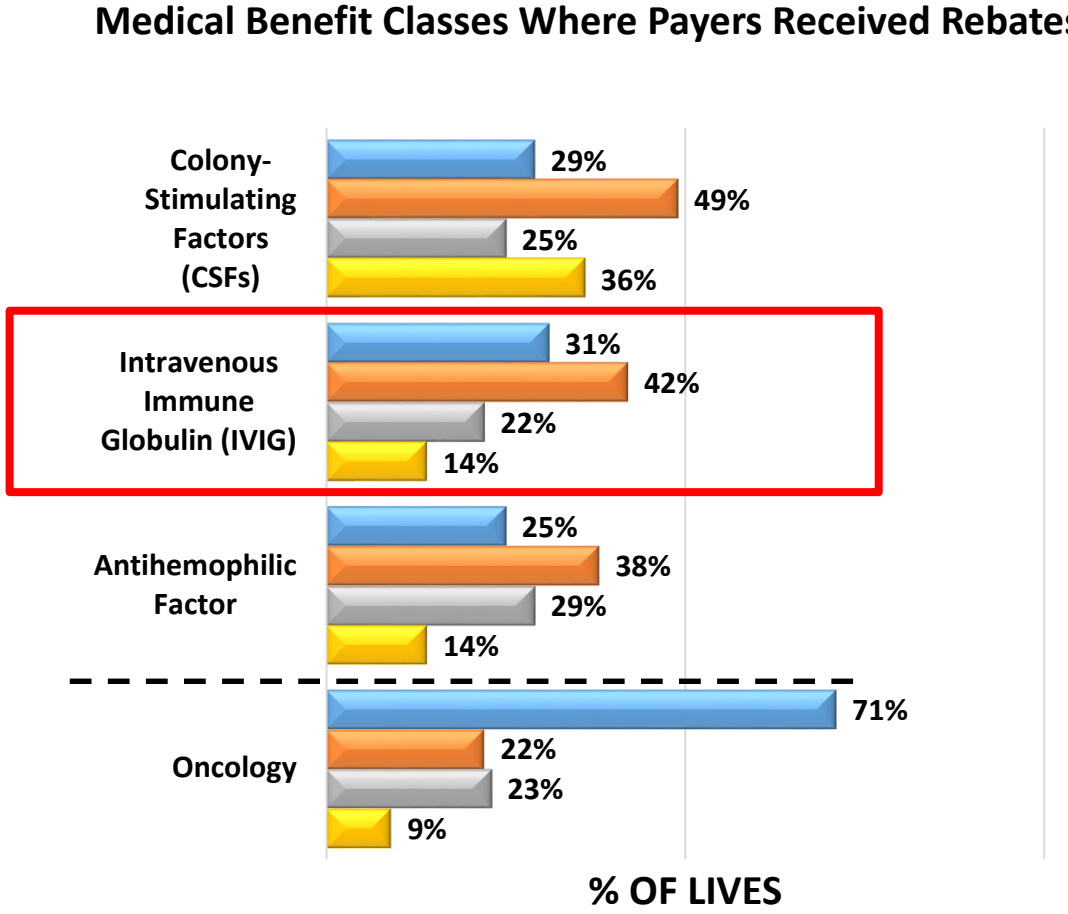


N=9 payors, 68 million covered lives (2014)

Magellan Pharmacy Solutions. Medical Pharmacy & Oncology Trend Report 2014.

While Product Preferencing for IVIG has Decreased, Rebates have Increased

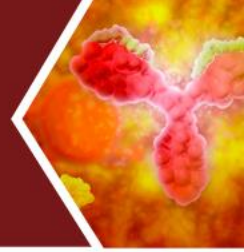




N=29 payors, 37 million covered lives (2011)
N=27 payors, 78 million covered lives (2012)
N=27 payors, 82 million covered lives (2013)
N=28 payors, 71 million covered lives (2014)

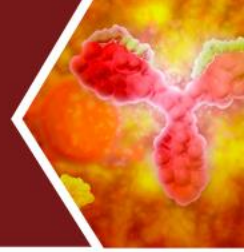
Magellan Pharmacy Solutions. Medical Pharmacy & Oncology Trend Report 2014.

Emerging Strategies May Play a Role in Future Ig Replacement Management Initiatives



- Value-based Benefit Design
- PBM-driven Management Programs
- Bundled Payments
- Better Care Coordination

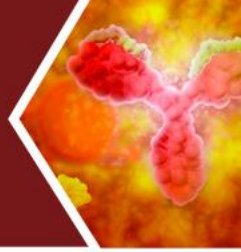
Value-based Benefit Design Has the Potential to Improve Outcomes and Spread Financial Risk



- Payers and independent companies use pharma-driven patient assistance programs to dictate copay level and benefit
- Specifically, value-based benefit design is the explicit use of member rewards and out-of-pocket contributions to create incentives for adoption of one or more of the following:
  - Use of high-value services, including certain preferred prescription drugs and preventive services
  - Adoption of healthy lifestyles, such as smoking cessation or increased physical activity
  - Use of high-performance providers who adhere to evidence-based treatment guidelines
- Most plans are already equipped to offer such a program

NBCH. http://www.npcnow.org/system/files/research/download/VBBD_Report_for_Health_Plans.pdf

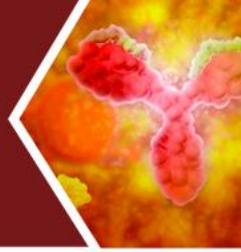
PBM-driven Programming Can Likewise Improve the Quality of Care and Associated Outcomes



- Medication therapy management (MTM) and similar programs offered through PBMs and specialty pharmacies can help identify drugs, dosing, and adherence based on claims data and payer data
- Such programs often incorporate an algorithmic loop of dose assessment, patient assessment, and physician engagement to ensure adherence to evidence-based guidelines
  - Utilizing professionally peer-reviewed information, clinicians can use the program to conduct specific pharmacy outreaches to patients at key intervals during their Ig therapy in order to provide timely education and treatment support
- MTM also monitors adherence and addresses adverse events which may adversely affect adherence to ensure the quality of care is not compromised
  - 80% of plans surveyed list measurement of adherence and persistency as the most valuable service offered through specialty pharmacy providers

EMD Serono Specialty Digest. 10th ed. Rockland, MA: EMD Serono, Inc; 2014. www.specialtydigest.emdserono.com.

A Medicare Demonstration Project is Underway to Evaluate the Use of Bundled Payments for IVIG

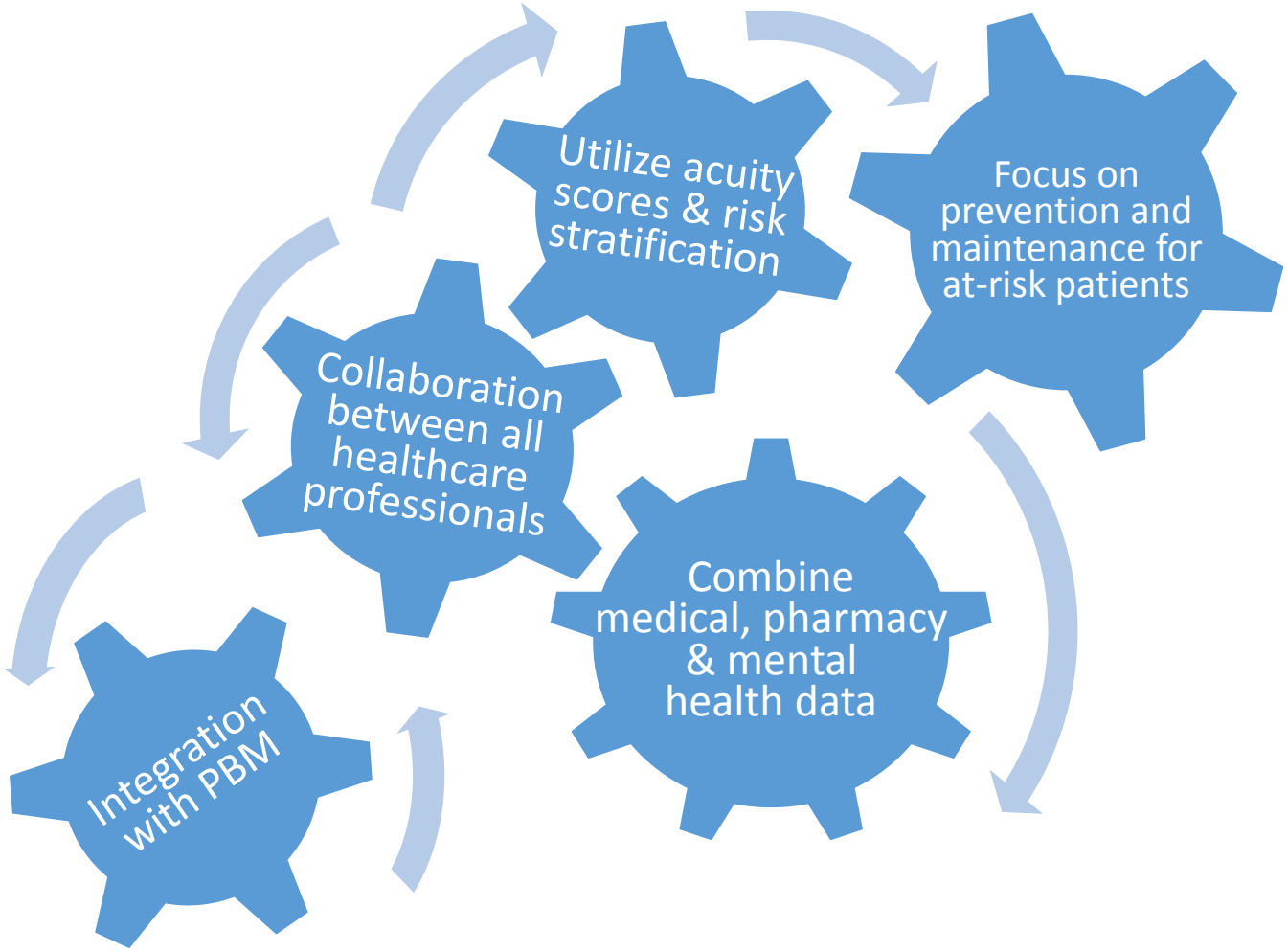


- The demonstration is being implemented to evaluate the benefits of providing payment and items for services needed for the in-home administration of IVIG for the treatment of PI
- Under the demonstration there will be a per-visit payment amount for items and services needed for the in-home administration of IVIG based on the national per visit low-utilization payment amount (LUPA) under the prospective payment system for home health services
- Under this demonstration, Medicare will provide a bundled payment under Part B for items and services that are necessary to administer IVIG in the home to enrolled beneficiaries who meet the following requirements:
  - Not otherwise homebound and receiving home health care benefits
  - Require IVIG for the treatment of PI, or currently receiving SCIG to treat PI and wish to switch to IVIG

CMS. Medicare IVIG Demonstration. http://innovation.cms.gov/initiatives/ivig/

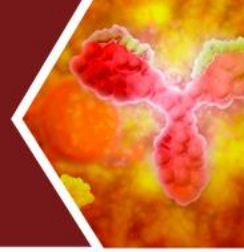
Integrated Care Management (ICM)

- Attention to prevention
  - Coordination with clients
  - Access to CM system
  - Customized reports
  - Patient engagement and accountability
  - Reportable outcomes



Pharmacy and medical expenses have a symbiotic relationship; collaboration can make a meaningful impact and lower overall plan expense.

Summary



- Payer drug management policies should be mindful of the AAAAI practice parameter for PI so as not to compromise patient care
- Specialty pharmacy management programming, including medication therapy management, can help to strike a balance between traditional utilization management interventions and robust medication adherence
- Sophisticated contracting arrangements based on comparative effectiveness research may allow for additional budget management while promoting improved outcomes
- Excessively restrictive formularies present potential health risks to patients since forced switching of Ig products, which are not interchangeable, is not clinically recommended

Effectiveness, Costs, and Results of Collaborative Care Approaches to Optimize Outcomes in

Antibody Replacement Therapy

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